PATHOLOGICAL NOTES

BY

J. GEORGE ADAMI, M.A., M.D., F.R.S.E.

FOR PRIVATE CIRCULATION

MONTREAL
JOHN LOVELL & SON, 23 to 31 ST. NICHOLAS ST.
1898

PREFACE.

The following pages contain abstracts of my lectures upon General Pathology, and are intended purely for the use of the students at McGill attending those lectures.

These abstracts have been dictated at odd times during the course of a very busy session, when often it has been impossible for me to thoroughly revise the proof and to make emendations. Thus, reading over the various lectures, I find much that I would like to put into a clearer form—much that I have left out in my attempt to be concise. Indeed, I would ask the members of the Class not to consider that these printed pages are intended to replace notes at lecture; so much is left out that notes must still be taken. Nor, again, are these pages intended to do away with the study of text-books. They will indicate the general treatment of the subject, and will be of aid in rendering the notes more comprehensible and in giving an orderly grasp of the subjects treated.

Just as in order to appreciate any object it is necessary to view it from several positions, so, in order to gain the most satisfactory understanding of a subject like Pathology, it is necessary to view it from the standpoint of different observers. The student is too apt to regard a printed book as infallible, and because a statement is written in a book—that is all-sufficient. If, however, instead of looking at one text-book on any subject, he dips into two or three, he will very soon learn that authorities differ, and in learning this, and in puzzling to explain real or apparent contradictions, he will gain the power of forming his own judgment, a power which appears to be sadly lacking in most of us mortals, and which once gained raises a man above the level of those with whom he comes into daily contact.

I would, therefore, urgently beg the men of the Third Year to utilise the time which may be saved to them in various ways by

the possession of these pages for reading up the subject in other authorities whose works may be borrowed from the College Library.

There has, I know, been a feeling expressed by some that the course of Pathology at McGill occupies relatively too important a place and too great an amount of time in the curriculum. This view, to say the least, is short-sighted, more especially when urged against a course of General Pathology, for general pathology is the basis of medicine, and not only of medicine proper, but of surgery, and of each and all the special numerous branches of each subject, and so in every individual case which presents itself to the medical man, a knowledge of the broad causes, progress and results of the processes of disease, and also of the probable effects of disease of one organ or system upon the rest of the body, is of enormous importance.

It is quite true that the ignorant and the quack can render himself rich, and it is true that he may manage to effect apparent or even real cures without knowing a word about the science of medicine, but the object of this, as of other University courses, is not to make a man rich, but is to make him thoughtful and useful to the community. Thus, then, at McGill our aim is, and must always be the aim, to turn out men who by their powers are a credit to themselves, their profession and the University, and to do this, the more thoroughly they are grounded in subjects like anatomy and pathology the greater is our success in attaining to our desires.

J. G. A.

INTRODUCTION.

Pathology, in its widest meaning, embraces the whole of the scientific treatment of medicine, save the discussion of the Treatment of Disease. It thus deals with.

The Causation of Disease,
The Course of Disease,
The Results of Disease.

According as to how these subjects are approached and treated, so are we accustomed to speak of them under varying names. We can attempt to classify and gain a broad general knowledge of the causation of disease, or can take up each disease recognized by us and give, or attempt to give, its etiology. We can similarly describe the course of each individual disease, giving its Symptomatology, or, on the other hand, can, from our knowledge of the course of the various diseases, attempt to distinguish certain morbid processes, one, or more than one of which is an evidence during the course of any given disease. And dealing with the results of disease we can either describe the effects of disease upon the various organs, or, on the other hand, can more especially discuss the broader subject of the general results of disturbed functions of one organ or system upon the rest of the organism.

In the following pages I shall take up the more general aspect of the subject, leaving the special and specific causes of specific diseases to be treated in text-books of Medicine and Bacteriology, in the former of which will also be found the symptomatology of the different specific diseases, while Special Pathological Anatomy or Histological Anatomy and Special Pathological Chemistry, or, as it is termed, Clinical Chemistry, forming, as they usually do nowadays, special courses, must be studied in those courses and in the many excellent text-books especially devoted to these sub-

jects. Even when all these are disposed of, the subject remains very large, and it will be seen that there is left to be treated the following :—

I. General Etiology.

II. The Morbid Processes.

III. The results of disease affecting the different systems upon the other systems and the organism as a whole.

PART I.

The Causes of Disease.

Disease and abnormal relationship of the organs may in the first place be due to some constitutional defect transmitted from the parent, and so, being due to the actual constitution of the individual, be of internal origin, or may again be the result of some influence affecting the individual. The more we consider the matter the more we must come to the conclusion that such influence must act from without and be of external origin. In other words, disease may be either INHERITED or ACQUIRED. These two forms of disease are in many respects so different that they may be considered separately.

INHERITED DISEASE.—The problems of heredity are very far from being solved, and there is very wide divergence of opinion with regard to their solution. Much has been thought and written concerning them during the last few years with the result that we seem to be, if anything, further from arriving at any settled views upon the subject. In the following paragraphs I will endeavour to bring forward briefly the main points bearing especially upon the inheritance of disease. To do this it will be best to begin with some of the simplest cases.

If we take the very simplest forms of life known to us, namely, the bacteria, forms so simple that in them there is no clear separation between nucleus and cell substance, we find in them that by external influence, by modification of their environment, we can without great difficulty bring about profound modification in their character. If, for example, we take a colour-producing form of bacillus, for example the bacillus prodigiosus, we can, by subjecting it to heat for a short time, heat which is just below that sufficient to kill the organism, prevent production of the colouring matter. We can so affect the bacilli that, if now we return them

to the ordinary temperature and ordinary condition of growth for long periods, and for it may be hundreds of generations, they are incapable of producing colour, and, instead of having a rich red colour, there is a succession of perfectly colourless growths. What has happened here has been that the individual subjected to the high temperature has been profoundly modified. In this low form there is no sexual reproduction; growth is by division, therefore the individual bacillus that has been thus modified divides into two; each half is half the original protoplasm of the parent, and possesses all the same features as did the parent, and when each of these halves again divide, its products of division continue to retain the character of the parent form. Sooner or later in such cases as these the power of pigment production may return. In other words, these modified forms again become so influenced by their environment that those most favourably situated reassume the power of pigment production, which thus must be considered as having lain dormant for long generations, and as having been called again into existence by favourable surroundings. In other cases, however, the alteration would seem to be more permanent, and definite races of bacteria presenting permanent deviations from the normal may develop. We can, for example, take the baccillus anthracis causing splenic fever, which in its most virulent condition will destroy cattle and men, and if we bring it outside the body, can so weaken its virulence that eventually we get an active growth which when inocculated will not kill the most susceptible animal with which we are acquainted, namely, the newborn mouse, and by no means in our power can we obtain restoration of virulence. Many other examples of this power of modifying the characters and even the form of bacteria by alterations of their environment might be brought forward, so many that evidently the only safe conclusion to reach is that external influence can act upon these low forms, and as a consequence there is transmission of acquired characters.

As we ascend the scale of life, we find that the conditions become more complex; in the first place, the cell unit presents division into nucleus and cell body; in the second place, sexual conjugation becomes the rule.

THE EFFECTS OF THE NUCLEUS.—All the studies made by cytologists prove conclusively that in unicellular organisms and the individual cells of multicellular organisms the nucleus is the controlling and directive factor in the life history. Take any large cell and cut it into two parts, one containing the nucleus, the other consisting only of cystoplasm or cell substance, and the latter part will inevitably die without sign of proliferation; the former under favourable conditions will live and eventually proliferate.

The nucleus, in fact, is the directive portion of the cell, and this is seen especially in the act of cell multiplication or more exactly in the most usual form of the same known as MITOSIS or indirect cell division. If we examine, for example, the course of events in the cells of the epithelium of the salamander, which forms one of the easiest and best tissues to study, we see that, long before there is any division of the cell, the more solid portion of the nucleus, that which especially takes on the nuclear stain and which is usually spoken of as chromatin, from forming an irregular network through the nuclear body, becomes formed into a chain or tangle. This chain now takes up the equatorial position in the cell and splits it into a series of perfectly equal portions, the number differing in different animals, and these portions are roughly ranged so as to form an equatorial star or aster. Next, each of these portions divides into two equal and similar halves producing a double star, and the two stars thus formed pass towards the opposite poles of the mother cell, and now the reverse series of changes occurs, the parts fuse into a tangle, etc. It is only after this separation that the cystoplasm of the mother cell separates into two and the daughter cells become evident as separate bodies each with a nucleus which is an exact half of the mother nucleus. *Nuclear division precedes cell division.*

Without dwelling fully upon the minutiæ of mitosis, it may safely be said that both in unicellular and multicellular organisms, inheritance, whether of normal or pathological conditions, must be largely dependent upon the nucleus.

THE EFFECT OF CONJUGATION AND OF SEX UPON INHERITANCE.

In this matter of inheritance sex introduces a further perturbing influence. What was the origin of the process of conjugation it is difficult to say; suffice it to say that we find it already present in the lowest forms, in nucleated unicellular individuals, and that from this point onwards it becomes the most common method of reproduction. In the earliest and lowest forms we observe that two like cells fuse into one; there is no distinction to be recognised between the two cells thus fusing. As we pass up to the metazoa—the multicellular organisms—we find that a distinction becomes markedly evident between the two, the one cell or ovum being receptive, the other cell or spermatozoon in the process of conjugation passing actively into the former and fusing with it. Both ovum and spermatozoon are formed of nucleus and cystoplasm. In the former, the cystoplasm is relatively abundant, and may, as in the ordinary hen's egg, be filled with food matter or yolk. In the spermatozoa, in the majority of animals, the solid or main portion of this minute cell is wholly nuclear in nature.

If now we follow out what happens when the spermatozoon finds its way into the ovum, we observe that we have to deal with, not a general fusion of spermatozoon and ovum, but with a special and very remarkable fusion of the nuclear portion of the spermatozoon with the nucleus of the ovum. The process here again is mainly one affecting nuclei, and just as in the ordinary cell division the chromatin of the mother cell became exactly divided between the two daughter cells, so here, in the process of sexual reproduction, do we find that the nucleus resulting from the fusion of the two sexual nuclei contains part for part equal amounts of the chromatin matter of these two nuclei. This is the farthest point to which we can so far proceed in the matter of heredity. We see, that is to say, that the fertilised cells from which the offspring develops contains equal portions of the nuclear material of two cells, the one of paternal, the other of maternal origin. Starting from this point we lead to the following conclusions :—

1. That the cells of the offspring, or, in other words, the whole body of the offspring, is equally derived from paternal and maternal sources.

2. That, while thus equally derived from these two sources, it does not follow that the paternal and maternal germ plasm have equal influence in determining the structure of the body as a whole and of the individual parts. As a matter of fact, it is a matter of common observation that in some individuals the paternal, in other the maternal, influence predominates. Each individual offspring of a given pair varies.

3. While this variation, as has been pointed out by Virchow, may be regarded as pathological in that each individual varies more or less from the normal, in ordinary language we do not speak of such variation between the individual members of a family or race as pathological unless it passes certain ill-defined limits.

4. If there is some marked and inherited variation from the normal in either parent, the offspring may either present that as markedly as did the parent, or at the other extreme there is a possibility that through the preponderant influence of the other parent's germ plasm that variation may not be marked. The tendency will be for this variation to present itself, but not quite to the same extent as in the parent showing it. Thus sexual conjugation may be regarded as a means to preserve the normal by the admixture of germ plasms continuing from generation to generation. The tendency is to preserve the general type of the race.

5. While thus under normal conditions strongly marked variation of type or defects tend by sexual reproduction to die out, a slight variation existing in both parents is liable to be intensified in the offspring.

6. In multicellular animals acquired defects and injuries are not transmitted as such to the offspring. If, for example, an arm be cut off or an eye be destroyed, either of those injuries does not act upon the germ plasm in either ovary or testis. The chromatin of the germinal cells has been derived by direct descent from the chromatin of the parents and grandparents, and thus in the off-

spring there will be no signs of these acquired defects in one or other parent.

7. While these defects themselves are not transmitted, it is possible, if not probable, that there may be transmission of *liability to disease*. We see this transmission of liability definitely inherited in many families, more especially to give the most strongly marked example in those suffering from some one or other form of nervous disease, or from hæmophilia or gout, etc., etc. But there may further be the inheritance of acquired liability to disease —the children of alcoholics, themselves strong and well built, are peculiarly liable to show weakened constitution, more especially weakened nervous system; they are liable to be vicious, epileptic or insane.

This possibility of the inheritance of acquired diatheses has been to a large extent overlooked. If an individual, to continue our example, is given to poisoning himself with alcohol, and alcohol circulates in the blood, it must affect all the tissues of the body, among them the germinal cells, and it is quite within the limits of possibility that the toxic affect of the alcohol may act upon ovum or spermatozoon sufficiently to lower its vitality, insufficiently to render it impotent and to kill it. Thus such ovum or spermatozoon in conjugation may be so enfeebled that the resulting individual in all its tissues is influenced by the lowered vitality of the original germ cell. Such a view would explain the development of the various diatheses.

Acquired Disease.

It will be seen from the above account that I have left out of the account several conditions, what are in common parlance most frequently spoken of as inherited disease. It must be clearly understood that diseases may be acquired through influences acting upon the embryo in utero and during the course of its development, or may be acquired during post-natal life. The former class of cases are frequently spoken of as being inherited. This they are not, and if any term is to be given to this class of cases, they should be spoken of as *congenital* diseases or, even better, as

diseases *acquired in utero*. Many examples of this can be given. If the progeny is born showing active small-pox or other infectious disease, the mother at the same time being the victim of that disease, that is not inherited, that is acquired, and to take the most important class of cases, it is in the highest degree improbable that the germ of syphilis is present in the ovum at the time of fertilisation or penetrates that along with the spermatozoon. It is difficult to conceive that so active a germ could be present in the minute human ovum, and could be transmitted in one or other of the early cell divisions of the ovum without its so modifying that cell as to lead to its destruction and the production of a monstrosity, if not to the complete death of the embryo. Thus, then, in all cases where the child is born showing signs of syphilis, we must believe that the infection has occurred during the later stages and not during the early stages of intra-uterine existence. The occasional birth of a child from a mother who shows no external signs of syphilis, the father being affected, must I think receive its true explanation not from the supposition that there is infection from the time of fertilisation, but that infection occurs at a later period through the placenta, there being in that region some localised syphilitic lesion or lesions.

Besides these infectious diseases there are numerous other conditions which may be acquired in utero before the individual begins to breathe and post-natal life has its origin. Thus there may be inflammatory processes within the womb, as, for example, there may be adhesions between the amnion and the fœtus leading to arrested development of one or other region, or traumatism may occur leading to amputation of the limbs, or, again, gross injuries may occur during the third stage of labour. These are but a few examples of diseased conditions acquired during antenatal life.

During post-natal life disease may be acquired in a great variety of ways; anything in short which influences the individual may under certain conditions be a cause of disease. A table of these causes classified variously according to the taste of the authors will be found in any text-book on general pathology

We may have physical, chemical and mechanical causes, or animate, and inanimate, the former including parasites and microbes. And, lastly, we have those diseased conditions induced by imperfect relationship between the various organs of the body, the diseased states for example set up by imperfect working of the nervous system. Although it is difficult to trace the connection in all cases, it may be laid down that with rare exceptions some external influence has induced the primary lesion.

These various causes may begin to act at any point where the cells of the body are in direct contact with external matter. Thus process of disease may originate not only upon the surface of the body but in connection with the respiratory, digestive, urinary, and genital tracts. Even in those cases in which there is apparently an inherited tendency towards nervous disease, it is in general some stimulus received from outside through some one of the organs of sense that may be regarded as so irritating the central nervous system as to set up a disordered working of the same.

In the lectures upon Infection, Fever, etc., I shall have more to say upon the way in which these various agencies originate disease.

Monstrosities and Teratomata.

Applying the above statements to the consideration of the development of monstrosities and malformations, it will be seen that these conditions, while of ante-natal origin, may be either inherited or acquired. The group of *inherited* conditions includes almost entirely if not wholly what we are accustomed to regard as malformations rather than monstrosities. Such conditions for example as supranumerary digits, hare-lip, hypospadias, are well known to tend to show themselves through several generations. They are all conditions of imperfect or sometimes redundant development, which originating from some unknown cause in one individual are repeated in the offspring of the same.

But many malformations and all the monstrosities appear to be *acquired* in utero. Experiments during the last few years have

shown that by placing the fertilized eggs of fishes and birds under unfavorable conditions, and even by acting upon these eggs with toxic substances, monstrous growths of one form or other can be obtained in quite a large proportion of the eggs so acted upon. It has been found for example that vigorous shaking of eggs during the period of first segmentation may lead to the two first products of segmentation of the original cell becoming separate, and each growing; twins are produced enclosed in a common sac. Also that if the injury done is not complete and the two products become not perfectly separated but remain adherent, then each part may develop to a greater or less extent, and that thus we can have double monstrosities united to each other, at the head, chest abdomen, or other region. Or again under certain abnormal conditions, one portion of the body may be common to two individuals, and thus monstrosities may be developed having two heads with only a common pelvis and lower extremities, the upper part of the body being bifid. In this way, therefore, accidents happening to the embryo at a very early period of its development cause a certain large class of monstrosities to develop.

1. The explanation here given of these monstrosities is not that accepted by all; according to certain French observers it has been clearly proved that in certain animals monstrosities of the nature of a more or less complete fusion of two individuals are produced not so much by mechanical irritation of the segmenting ovum as by what is known as polyspermy, *i. e.*, they are due to the fertilisation of the ovum by more than one spermatozoon, as a consequence of which the ovum tends to undergo a double segmentation or to develop two or more individuals. The facts in support of this theory are still so few that I am inclined to consider it still debatable.

2. A further series of experiments upon the eggs of amphibia, fishes, etc., indicate another method whereby monsters—defective monsters—are produced. It has been shown that if one of the cells in the ovum which has segmented into 8 or 16 parts be carefully destroyed, as per example by a hot needle, the result

is very remarkable; animals so treated develop with one extremity wanting or one-half of the head and so on. Apparently each individual cell of the segmenting ovum in the early stage is destined to form the frame work at least of one definite portion of the body. It is difficult to cite clear and undoubted examples of such local disturbance and death of one of the earliest cells in the human ovum, but it is possible that some cases of anencephaly are of this nature, as I shall point out later; the majority of these may be explained in another way.

3. In other cases there has seemed to be an arrest of development of sundry cells; for example, certain of the median tissues of the head may be imperfectly developed, and thus, for instance, the nose be almost wanting and the orbits fused into one, there being but a single eye. There are a fair number of monsters showing this tendency towards fusion of two parts of the body.

4. Dareste and other French observers have pointed out from the observations upon birds' eggs that other defects of development may be brought about by the imperfect development of the amniotic folds. These may not completely extend over the whole of the developing embryo, and where they do not extend, or, again, where they become adherent to the embryo, their growth is arrested, and we thus have many varieties of anencephalic monsters.

5. Even later in development, amniotic folds and bands due to some inflammatory disturbance may become adherent to the limbs and cause arrested development and even amputation of the same.

Fever.

DEFINITION.— *Fever is a condition characterised by increased temperature of the body with disturbed metabolism in the various tissues.* It would perhaps be better to consider this under the heading of Infection, for most fevers are due to infection, but what is clinically recognised as Fever may be present apart from Infection. The disturbed metabolism is especially shown by *increased nitrogenous products given off in Urine, increased Co_2 given off* and by rapid emaciation.

A typical (Infective) fever presents the following stages:—

(1) PYROGENETIC, vessels of skin contracted, relative coldness of skin giving the sensation of cold and *chill*. The sensation of cold may be so great that *rigors* show themselves, *i.e.*, the muscles of face, extremities, etc., contract involuntarily, causing irregular fibrillary twitchings. During this stage internal organs are congested and rectal temperature may be two or three degrees higher than axillary, and may be raised to 103° or 104° or even higher.

(2) FASTIGIUM. The temperature of all parts of the body increased, vessels of surface more dilated, the skin in consequence hot and dry. This stage may continue for some little time. Temperature of all parts some three to seven degrees above the normal for each part.

(3) DEFERVESCENCE, this may be gradual (by *lysis*) or rapid (by *crisis*). Skin greatly flushed, and as a consequence great increase in heat given off, abundant perspiration and further cooling by evaporation of sweat. Temperature falls to normal.

DEGREES OF FEVER.

Subfebrile, 99.5—100.4.
Moderate Fever, between this and 103.
High Fever, 103 morning, 104 evening.
Hyperpyrexia, 107.5 and over.

Highest febril temperature noted (of 112.5) in a case of tetanus by Wunderlich: highest clear case of hyperpyrexia due to nervous disturbance (120°) recorded by Teale in case of fracture of vertebral column.

Varieties of Fever.

(*a*). Inflammatory or sthenic: chill and rigors followed by high temperature, hot and dry skin, pains in limbs, frequent strong pulse, great digestive disturbances, abundant urates, restlessness and delirium.

(*b*). Asthenic or Adynamic; great weakness, febrile reaction not prominent, tongue continues moist; may be nocturnal delirium.

(*c*). Typhoid or Ataxic, great perspiration, tongue dry, brown or black; sordes; heart's action impaired; pulse rapid, weak, compressible, dicrotic; bed sores; before death capillary congestion and cold sweats, muttering delirium, stupor, coma and exhaustion.

(*d*). Malignant, associated with multiple hæmorrhages and petechiæ; death within a few hours.

(*e*). Hectic; Remittent or intermittent, temperature, generally slight evening rise, where well developed frequent chills and rigors followed by much heat of skin, then profuse nocturnal sweats. Such hectic fever now attributed to secondary infection in course of exhausting diseases such as Tuberculosis.

(*f*.) Fever due primarily to Nervous Diseases, *e.g.* after injuries to head, cerebral tumours, etc. Great and continued rise of body temperature without corresponding increase in pulse and respiration.

(*g*). Post-Hæmorrhagic.

Causation of Fever.

(*a*). Majority of cases associated with infection.

(*b*). Some few cases due to nervous diseases as above mentioned, without infection.

(*c*). Other cases due to products of tissue destruction, notably in cases of internal hæmorrhages.

(*d*). Others due to chemical substances or poisons, *e.g.*, Phosphorus and cocaine.

What then is the exact nature of the febrile state? We can cause it experimentally in two or three ways: 1. Can inject certain pathogenic bacteria (but not all; *e.g.*, sp. choleræ cause no

fever.) 2. The products of bacterial growth. Either of these lead to typical fever, often proceeded by temporary lowering of temperature. 3. Can cause it by injection of bodies of the nature of ferments : fibrin, pepsin, rennet ferment, etc., etc. (Hildebrandt). 4. Can cause it by injections of extracts of muscle, kidney and other tissues, urine, etc., probably affected by retained blood after hæmorrhage due to action of fibrin ferment. 5. Can produce it by placing whole animal in chamber with temperature above that of blood (43°C. and over, or portion of animal, limb, etc., in greatly heated air chamber (100 to 150°C.) (Such fever, however, not characterised by successive stages seen in typical fever, but showing well marked evidences of increased metabolism.) 6. (*a*) By puncture (? destruction) of inner side of corpus striatum (Arohnson & Sachs). (*b*) ditto of anterior end of optic thalamus (Ott). (*c*) By injury to cerebral cortex immediately behind Fissure of Rolando. (H. C. Wood.). 7. By action of certain drugs *e.g.*, Phosphorus and Cocaine.

From these observations it is evident that there are two possible main theories explaining the increased temperature and increased metabolism of fever. (*a*) That centres governing the heat regulation of the body may be either primarily affected (by injury) or may be secondarily affected (by ferments, toxins, etc.), so that increased temperature of the body results. Or (*b*) that whereas the heat regulating centres may, under some cirsumstances lead to this increased temperature, in other cases the ferment-like bodies toxins or drugs, circulating in the blood may directly stimulate cells of various tissues, thereby leading to increased metabolism, and so to increased giving off of heat and increased temperature and febrile phenomena.

With our present knowledge we cannot state absolutely which of these theories is the correct one. By analogy with what occurs in inflammation, the second thory would appear to be the more probable. We know, for example, that phosphorus would seem to act directly in cells of liver and kidney, leading to extreme breaking down and degeneration of these cells. And the fact that the cells of these and other heat producing organs show such marked changes in infective fever would also seem to indicate that these cells are acted on directly by toxines. Still similar

changes may be produced in these cells without marked rise of temperature.

Difficulties in Connection with Nervous Theories.

Increased development of heat in body and increased temperature might be due to (*a*) arrested action of centre inhibiting heat production (inhibitory thermogenic centre), *i.e.*, centre ordinarily checking heat production is thrown out of gear, and heat production is unchecked. (*b*) Might be due to arrested action of centre causing loss of heat (thermolytic). In fever, such centre might be out of gear, therefore less heat given off: therefore increased storing of heat in body. (*c*) Might be due to stimulation of thermogenic centre. (*d*) There might be complicated mechanism of both thermogenic and thermolytic centres.

We have no clear evidence as to the exact nature and working of the heat regulating centres in the brain, all we can say is that we have abundant evidence of the existence of a very delicate means of heat regulation, presumably by more than one centre, *e.g.*, in the healthy individual, whether the surrounding air has a temperature of — 40° or + 120°F., the temperature of the body scarce varies one degree.

On the Relationship of Heat Production to Temperature of Body.

The temperature of the body depends upon the ratio between the amount of heat produced during a given period and the amount lost during that period. Thus, with a lessened heat production but more complete conservation of that produced, the temperature might be higher than would occur with increased production and increased loss of heat. Thermometric observations do not give us indication of heat production; for this we need calorimetric studies.

In the body, heat production is mainly due to metabolism of tissues, notably of muscles, heart, liver and large viscera, heat loss occurs mainly from skin, by radiation and evaporation, and from the lungs by heating expired air. There has been great debate as to whether in fever there is increased production of heat

or merely a lessened giving off of heat and so in either case increased temperature. On the whole the acceptable view is that there is some increased production, even though during the pyrogenetic stage there is evidence of lessened loss. In the febrile stage proper, Liebermeister found that patients with temperature of 104° and over placed in cool bath gave off twice as much heat as the normal individual. The increased metabolism in fever indicates this also. There is increased production of CO_2, increased consumption of O, increased production of urea and rapid wasting of tissues, of body all indicating such increased use of the tissues and presumably increased giving off of heat in this act. The heart beats more rapidly, the respiratory act is more rapid, and even though, there is great diminution in the amount of food taken, this is certain that if there is not in all cases a marked absolute increase of heat production, there is a relative increase.

Effects of Fever upon Tissues.

The most marked affects are cloudy, and if continued, fatty degenerations of various tissues with later, diminution in size and actual atrophy of component cells. Note also the arrest of digestive functions, catarrh of intestinal tract, etc. If fever rises above 107 the protoplasm of cells appears to become rapidly disorganised.

Meaning of Febrile Process.

We know little absolutely as to its meaning. This, however, is fairly well established that if the inoculation of an animal with certain pathogenic bacteria, leads to no proper febrile reaction or to an actual and continued lowering of temperature, the outlook is very bad ; on the contrary, a good febrile reaction is an indication which is on the whole favorable. When we consider the dangers of hyperpyrexia, this statement may seem paradoxical, however, safety in general appears to lie in a mean course, either poor reaction or excessive reaction may be dangerous. Recent researches have further shown that with the development of fever, certain substances appear in the blood which have antitoxic and even antibacterial properties. That the increased temperature is

in itself an agent in arresting the growth of pathogenic microbes, we have no satisfactory evidence, the evidence would rather seem to point to the increased temperature acting indirectly, viz., favoring the production within the system of certain antitoxic and antibacterial substances, and it may be stimulating the sundry centres in the brain and thereby leading to altered metabolism in the areas governed by these. Filehne has shown that streptococcic infection in the rabbit runs a more favorable course when the animal is subjected to a high temperature than when it is subjected to a low one, *i.e.* to an external temperature sufficiently high to raise the general body temperature, rather than to one sufficiently low to lower the body temperature.

NOTE.—While on the subject of Fever consult some text-book of Physiology for data bearing upon: normal temperature: diurnal variations of temperature: variations in normal temperature at different life periods: effects of variations in external temperature upon body temperature: effects of food in body temperature: theories of temperature regulations.

Intoxication.

DEFINITION.—Under this heading we group together the changes in the system brought about by substances which, gaining admission into the system by means of the blood, lead to definite impairment of health. Note that the term indicates a *general systemic disturbance* as contrasted with local action. The substances which lead to such intoxication are *poisons*. There is no one word to express the local actions of these poisons, but between this local action and intoxication there is the same distinction as between inflammation and infection.

These poisons act very variously and are of all varieties: (1) *Mineral*, including also the artificially produced carbon compounds and gases; (2) *Vegetable* products (mainly alkaloids and glucosides). Here also we must include the toxines of bacteria. (3) *Animal* products, including ptomaines, leucomaines and the specific poisons of various animals, *e.g.*, the secretions from the poison glands of snakes and serpents, from the stings of bees, wasps, etc., and the poison glands of spiders, cutaneous glands of toads (Phrynin) and cantharidin (from the beetle, *Lytta vesicatoria*, the Spanish fly), etc., etc. It is, however, next to impossible for us to classify the poisons in this way. The proper pathological classification is according to the effects produced.

Such effects are twofold (1) *local*, at the point of application and (2) *general*, the true intoxication. There is one marked exception to this rule, viz.: the case of H C N, which given in sufficiently large quantities may cause immediate death without permitting time for local effects to show themselves.

LOCAL EFFECTS OF POISONS.

The local effects may be of the nature of (*a*):—Corrosive and acute necrotic disturbances, *e.g.*, those brought about by corrosive acids, alkalies and salts of various metals, including Sb., Hg., Ag., Zn., Cu. and Fe., with a more or less extensive

necrosis. If there has been time for reaction there is more or less evidence of surrounding inflammation. (*b*) :—Irritation and inflammation of tissue. Many substances do not cause so severe disturbances, but set up local irritation of tissue with inflammation ; this is especially to be noticed in connection with toxic substances derived from animals and vegetables and the gaseous substances which cause irritation, especially of the mucous membranes of the eye and respiratory system.

General Effects of Intoxication.

The general effects may show themselves more especially upon

(A) The blood.

(B) The organs of circulation.

(C) The nervous system,

(D) The alimentary system.

The effects on the various systems are capable of all forms of combination in different forms of intoxication.

A. Effects on the Blood.

These may be of different types: (1) The poison may act especially upon the hæmoglobin, *e.g.*, CO poisoning depends mainly upon the combination which CO forms with the hæmoglobin. It is essentially a tissue asphyxia, though nervous disturbances also supervene. HCN in not too large doses appears also to join with the hæmoglobin, forming a relatively stable *cyanmethæmoglobin;* in larger doses it acts directly on the nervous system causing paralysis. Similarly H_2S forms *sulphurmethæmoglobin.*

(2) The second group of substances form methæmoglobin and at the same time lead to great destruction of the red corpuscles, *e.g.*, oxidizing substances, ozone, chlorates, nitrites and nitrates, reducing substances, and some of the aniline salts. *Methæmoglobin* is a more stable compound of oxygen with hæmoglobin than is the ordinary oxyhæmoglobin. Here, again we have a tissue asphyxiation, along with other complications.

(3) Poisons which more especially act upon the serum and (?) white corpuscles leading to spontaneous coagulation of the blood in the vessels. (*Abrin* and *Ricin.*) With or without this liberation of the fibrin ferment, there seems in connection with these substances, as also in connection with some of the animal poisons, to be a destruction of the antibacterial and antitoxic substances in the blood, so that proliferation of bacteria rapidly ensues within the blood vessels. According to Saranelli the toxine of yellow fever seems also to favour the growth of other microbes throughout the system.

B. C. POISONS OF THE ORGANS OF CIRCULATION AND OF THE NERVOUS SYSTEM.

It is difficult to dissociate these two: certain substances, however, appear to act directly upon the heart muscle (*e.g.*, *digitalin strophanthin* and *muscarine*) and some like *ergotine* act directly upon the vessel walls. A very large number of poisons act especially upon the nervous system, producing death through paralysis, *e.g.*, *chloroform* (vide Dr. Waller's paper, B.M.J., Nov. 20, 1897), *alcohol*, the *hypnotics*, *cocaine* (which with *curare* acts especially on the nerve endings) and *strychnine* (which especially causes stimulation and irritability of the nerve cells.)

D. POISONS ACTING UPON THE ALIMENTARY SYSTEM.

A very large number of toxic substances apparently are absorbed through the alimentary canal. Such poisons may cause temporary local disturbance, and in the main tend to be arrested and excreted by the liver. They directly set up irritative changes in these organs. Other poisons set up irritative disturbances in the intestines in the process of being excreted therefrom. Hg., Sb., and the toxine of yellow fever (?) seem to act in this way.

Note also that intoxication may be acute or chronic, and that the manifestations will differ according as to whether one large dose has been taken or whether small quantities are being frequently absorbed (*e.g.*, look up arsenic poisoning in some late text-book of Toxicology).

AUTO-INTOXICATON.

Considerable attention has of late been directed to this subject. The human organism may be poisoned by the products of its own digestive metabolic processes. These substances (*a*) may be normally found in the body, but may accumulate in excess, or (*b*) may be those which are not known to occur normally, *e.g.* (*a*) The products of putrefactive decomposition in the intestine *indol*, *phenol*, etc., *bile salts* in the blood in obstructive jaundice. (*b*) The oxybutyric acid of diabetes, the diamines of cystinuria, etc.

Much of the experimental work performed in this direction is not satisfactory; the supposed poisons have not been accurately separated; it is obvious, however, that the condition does exist, thus for example, in *hydrothionæmia*, it is known that H_2S is produced in the intestines in considerable amount, that it appears in the urine, and that, when H_2S is introduced into the blood of animals, symptoms result resembling those of *hydrothionæmia* (headache, giddiness, delirium, exaltation, collapse). So also we can experimentally show the dependence of some of the constitutional symptoms of acute obstructive jaundice upon the bile salts which accumulate in the blood; and further it is evident that the symptoms of uræmia are due to auto-intoxication, to failure of the kidneys to excrete certain substances.

We may perhaps with safety divide these auto-intoxications into two groups, the *intestinal* and the *metabolic*. Most of the intestinal are doubtfully auto-intoxications and are more nearly allied to the infections, *i.e.*, to the systemic disturbances produced by bacterial products. At the same time it is possible that many of the metabolic auto-intoxications are primarily set up by intestinal disturbances, *e.g.*, increased excretion of uric acid both in the course of infectious diseases and in conditions of gout, etc., seems to be associated with intestinal derangement if not originated thereby.

Infection.

DEFINITION.—Infection is the succession of changes produced in the system in general by the entry into the tissues and proliferation there of micro-organisms. By analogy the term also includes like disturbances occurring in the system in states in which the pathogenic microbes have not as yet been discovered, but which so closely resemble those caused by pathogenic microbes that we believe them to have a like origin (the acute exanthemata in general syphilis, etc.).

In inflammation we have largely, though not entirely, to deal with the local effects of such pathogenic micro-organisms. In infection we have to deal with the general effects upon the system. It may be noted that associated with infection there may be numerous foci of inflammation *e.g.*, in tuberculosis and small-pox) or only a single focus (as in tetanus).

In old works in Medicine and Pathology a distinction is generally made between contagious and miasmatic diseases. The distinction does not hold. By *contagion* is understood the passage of the infective virus from individual to individual. By *miasm* an infective virus derived from water or soil, as, for example, the microbes of malaria and to a large extent of typhoid. We now know that in the case of a very large number of diseases the germ may at one time pass direct from one individual to another, at another by the intermediation of the external world, there being a longer or shorter period during which the germ exists outside the body; this being the case, it is well to do away with the distinction.

ENTRY OF THE INFECTIOUS AGENT INTO THE SYSTEM.

Entry may be from any of the surfaces of the body. (*a*) Skin. (*b*) Respiratory tract. (*c*) Digestive tract. (*d*) Genito-Urinary.

CONDITIONS UNDER WHICH GERMS ENTER.

Under ordinary conditions the epithelial covering of the skin and mucous membranes forms a first line of defence, and so long as ths is intact and healthy, for so long germs cannot penetrate

Exceptions to this: we not unfrequently come across cases in which we find the mucous membrane of the intestines intact, or again find absence of disease of the lungs and yet the mesenteric and peribronchial glands respectively are the seat and apparently the starting point of diseases produced by bacteria. The explanation is apparently that leucocytes can wander between the covering cells of mucous membranes and may pass back bearing with them infective microbes, and these microbes may be carried without trace of their passage to the nearest lymphatic glands.

The various lymphatic glands and lymphoid tissue in general appear to form a second line of defence in very many instances. It is when the cutaneous or mucous surfaces fail to arrest pathogenic bacteria, and when these gain an entrance into the tissues that we obtain the first stage in infection, local proliferation and local inflammation.

Nevertheless, fever and the evidences of infection in general show themselves before the pathogenic microbes have undergone more than a local proliferation, *e. g.*, a simple carbuncle on the nose or a simple "sore throat" may be associated with marked fever and malaise. In either of these cases the bacteria remain purely local. Examples of a slightly different order are to be seen in tetanus and the majority of cases of diphtheria. In the two conditions the pathogenic bacteria have purely a local growth. So long as the local disturbances predominate and the general effects of the toxines are slight, we have what is known as the *incubation* stage of an infection.

See note book more explicit

Explanation of Symptoms of Infection.

The last cases mentioned indicate clearly that the main symptoms of infection are due to the products of bacterial growth, and we can reproduce most of the symptoms if not all by injecting into animals the culture media in which bacteria have grown and from which those bacteria have been filtered, or again, culture media in which the bacteria have been killed by volatile disinfectants.

Nature of these Products of Bacterial Growth.

It is difficult to say anything absolute, save that: (1) Whatever their composition, they are present in extremely minute quantities.

(2) That they are diffusible.

(3) That they seem to be in the body in association with proteids and more especially with albumoses. Roux and Sidney Martin from their properties are rather inclined to consider them as being of the nature of ferments.

(4) It is possible that in each case we deal not with one but with more than one body (*e.g.*, Hunter's studies upon *tuberculin*).

(5) The products of the different specific infective bacteria differ. Most of them cause rise of temperature with all the symptoms of fever. Some, like those of cholera, produce no fever. Some seem to act directly on the tissues, here and there producing localised necroses (diphtheria, typhoid and tuberculosis). The action of the toxines of tetanus upon the central nervous system is very marked; the toxines of diphtheria seem liable to pick out and affect peripheral nerves, etc.

The relative part played by the effects of these toxines upon the nerves and upon the individual tissues respectively is a matter concerning which we have no definite information. It is difficult, however, to regard the extensive intestinal disturbances and degenerations of liver and kidney cells seen in yellow-fever, for example, as other than direct effects of the toxines.

Course of Infection.

Infection may lead to *death* or to *recovery*. It may be *acute* or *chronic* (as is more especially the case in those affections leading to granulomatous or tubercular new growths, tuberculosis, glanders, leprosy and actinomycocis).

Theories to Explain Recovery.

It is difficult to understand at first sight why, if once the pathogenic microbe enters the body and begins to proliferate, it does

not continue to grow until by its growth and products it leads to death. The older writers thought that recovery was due to the fact that the bacteria in growing had exhausted all the available food-stuffs; or again that the bacteria were arrested by the products of their growth. Neither of these theories is satisfactory, because a given pathogenic bacteria microbe, *e.g.*, B. Anthracis, will grow perfectly well on the body fluids of animals dying from diseases caused by that microbe. We now know that the body produces substances either antibacterial or antitoxic. It is generally held now-a-days that, with the growth of the pathogenic microbe in the body, a reaction is set up leading to the increased production of these anti-bodies, and that it is the gradual accumulation of these which eventually results in the destruction of the products of growth of the bacteria and the death of the bacteria themselves.

Immunity.

DEFINITION.—Immunity is a term which may be employed either to cover the whole class of cases in which there is an *insusceptibility to poisons*, whether these be bacterial toxins or mineral, vegetable or animal poisons in general. Or, on the other hand, it may, as is most frequent nowadays, be used to indicate that condition of the system of the animal in which microbes are incapable of growing in the tissues and of setting up infection. Insusceptibility to poisons in the broadest sense of the term may be either *inherited* or *acquired*.

Among the examples of *inherited immunity* may be mentioned the fact that the bacillus of anthrax has no effect upon white rats, while the cocco-bacillus of Rabbit septicæmia does not affect rats, guinea pigs or dogs, while many of the microbes causing epidemics among the lower animals are never found growing in the human tissues.

There may be marked differences noticeable among the individuals of different varieties of the same species; black dogs are more susceptible to anthrax than other members of the canine species. So also, while ordinary sheep are very susceptible to this same disease, Algerian sheep are relatively insusceptible. White men are much more susceptible to yellow fever than are negroes.

Acquired insusceptibility to poisons and immunity may be brought about in more than one way. Thus, many diseases are liable to affect the young individuals of man and other species, while adult animals, although they have never had an attack of the disease, become immune. Or again, while a newcomer to a district is liable to certain diseases peculiar to that district, the older resident becomes *acclimatised*, although he too may never have shown signs of disease, *e.g.*, malaria, black water and other tropical diseases. Such immunity may also show itself in the course of a few generations, *e.g.*, throughout the civilised world there is a partial immunity to measles, a disease which in its first

entry into a country (Iceland and the Pacific Islands) causes an enormous mortality.

The most remarkable examples of acquired immunity are, however, to be seen in those cases in which one attack of an infectious disease protects the system against further attacks, *e.g.*, small-pox and the acute exanthemata in general.

Acquired Insusceptibility to other Poisons.

What is true with regard to many infectious diseases is true also with regard to certain poisons of other nature. Thus, by continually taking small doses of arsenious acid, the mountaineer of Styria can take daily as much of this intense poison as would suffice to kill numerous healthy individuals. Opium eaters and drinkers and chronic morphinists show the same powers. While, by frequent injection, animals can be rendered immune towards vegetable poisons like abrin and ricin and, as Calmette has shown, against snake poison.

On the Nature of Immunity towards Infectious Diseases.

These observations upon non-bacterial poisons show that the tissues of the body can by training be habituated to the presence of poisons which at first in small quantities are capable of so disturbing the functions of those tissues that death ensues. They show further that in connection with bacterial toxins, as with other poisons, there are two possibilities:

(*a*) That the tissues gain the property of forming substances which counteract the poisons.

(*b*) That whereas the poison when first introduced into the system may set up intense molecular disturbance in one or other tissue; at a later period the same poison sets up less molecular disturbance and may (without antitoxins being of necessity developed to counteract the poison) become relatively harmless, and now when present in the system in larger proportions than it was at first may fail to stimulate or irritate the cells to the same extent, *i.e.*, the boy that is frequently thrashed does not feel

the stimulus so acutely as the boy who receives his first thrashing. It is possible that this second explanation is not sufficiently employed at the present time to explain acquired immunity against infection.

Theories with Regard to Acquired Immunity.

I have already treated this subject to some slight extent in the lectures upon Inflammation. Suffice it to say that the older theories with regard to using up of food stuffs suitable for the growth of bacteria do not hold. That more recent observations show that where once the animal has suffered from a disease there is in most cases a tendency to the development of a more rapid reaction at the point of entry of the bacteria; more rapid congestion of the vessels and diapedesis of leucocytes with more rapid destruction of the invading bacteria. *Immunity*, in the words of Metchnikoff, *is but recovery in operation from the very onset of the disease.* Further, it must be noted that during the progress of a disease, as already mentioned in a previous lecture there appear in the fluids of the body certain sundry antitoxic and antibacterial products. It may be urged that the development of these and their existence in the blood and tissues is the main cause of immunity, but the evidence forthcoming up to the present time would seem to indicate that these antitoxic bodies gradually disappear from the blood without the insusceptibility of the animal to a given disease being lessened, *i.e.*, we lack evidence to show that the antitoxic and antibacterial properties of the blood bear a fixed ratio to the degree of immunity against a given disease possessed by the individual. Immunity then does not depend primarily upon the constant circulation of these bodies.

(Look up the modes of rendering animals immune against poisons and other aspects of this subject in bacteriology notes.)

Internal Secretion.

We have now abundant evidence that many of the glands of the body, both those possessing excretory ducts and those which are ductless, elaborate sundry diffusible substances or secretions which pass into the blood and lymph and are absolutely essential for the proper performance of the bodily functions.

EXAMPLES.

1. The liver, besides excreting bile into the bile ducts, undoubtedly plays a large part in the formation of urea, and again in regulating and giving off carbo-hydrate substances into the blood.

2. In the absence of the pancreas there is a great accumulation of sugar in the blood, and the only satisfactory explanation of this accumulation of sugar is that the healthy pancreas supplies to the blood some glycolytic substance which under normal conditions breaks down the sugars.

3. If the thyroid gland be extirpated, more especially in carnivorous and omnivorous animals, there is developed a curious condition known as Cachexia Thyreopriva, the symptoms of which are great mental disturbance, tremors, falling out of hair and a somewhat unusual form of œdema of the skin. If into animals deprived of the thyroid there be injected an extract from the gland, these symptoms do not appear. It is evident, therefore, that there is something in this extract and something in the normal internal secretion of the gland which prevents this chain of symptoms. A chain practically identical with the symptoms in animals is seen in man in cases in which, post mortem, the thyroid is found greatly atrophied, and again after the surgical removal of the whole gland. This condition first described by Ord is known as Myxœdema. (For full symptomology see Textbook of Medicine.)

4. Schäfer and Oliver have shown that the extract of the medulla of the suprarenal bodies causes among other things a profound rise of arterial pressure and evidences of greatly increased tonus of the heart and arteries. In cases in which the suprarenals are atrophied or destroyed the exact opposite is seen, the pulse very feeble, the blood pressure low and the heart beats very weak. From this it would seem evident that the suprarenals among other things elaborate an internal secretion which counteracts some substance depressing the heart, or leading to the diminished tonus of the arteries, or both.

5. There is a certain amount of evidence that the pituitary body also gives off an internal secretion, for when this is greatly diseased we frequently find the development of a condition known as Acromegaly. (For symptoms see Textbook of Medicine.)

6. Certain authorities also hold that the testicles and ovaries give off an internal secretion; the evidence here is, however, not very strong at present.

Mode of Action of the Internal Secretion.

It is evident that if these substances pass into the blood from these various glands, and those glands are in a healthy condition their action must be to counteract and break up substances which are harmful to the economy, because we find that where the internal secretions are wanting we get the above described conditions of disease, which are really conditions of auto-intoxication. The health of the body therefore would seem to depend *inter alia* upon a due balance between the *internal secretions* and the *toxic substances upon which they act.* If this be so it is possible that similar symptoms will result from either:—

(*a*) Disease of organ supplying internal secretion, with diminished secretion, or—

(*b*) No disease of organ supplying internal secretion but excessive production of the toxic substance or substances upon which it acts.

In the former case we should find well-marked anatomical disturbances in the special gland, and in the latter case we should

not necessarily find any such disturbance. As a matter of fact this absence or presence of lesions of special organs is a marked feature in several diseases of the nature here referred to. Thus in diabetes sometimes the pancreas is gravely injured and sometimes it seems quite healthy. We occasionally have Addison's disease without any sign of morbid change in the suprarenal, and, in myxœdema, more rarely the change in the thyroid does not appear to correspond to the severity of the symptoms.

Excessive Internal Secretion.

In the second place it is possible that excessive production of internal secretion may also lead to that disturbed equilibrium of the system which we know as disease. It has been found, for example, that, if patients be given either subcutaneously or by the mouth too large a quantity of thyroid juice, they exhibit pronounced disturbance. This hyperthyroidism shows itself in more rapid pulse, emaciation and signs of mental irritability. A somewhat similar train of symptoms is to be recognised in the condition of *Exophthalmic goître* or Grave's Disease, in which, as Greenfield more especially has pointed out anatomically, the thyroid shows signs of overgrowth and increased activity and proliferation of the glandular cells.

(It must, however, be borne in mind that administration of Thyroid Extract never causes the whole body of symptoms characterising Grave's Disease, *e. g.*, the *Exophthalmos* is always wanting.)

Compensation.

The difficulty which arises in the anatomical study of these cases, which seem to be of the nature of disturbed internal secretion or of alteration in the amount of toxic substances acted upon by the secretions, is that we may meet with diseased states of these various glands unaccompanied by any recognisable symptoms. We have evidences in many instances where the gland becomes not too rapidly involved that there may be set up *compensation*, other glands manifesting what is known as *vicarious*

activity. Thus when the thyroid is diseased, the pituitary body is often found enlarged; where the pancreas is diseased, some authorities have recognised the enlargement of Brunner's glands in the duodenum; or again we have the more familiar examples in paired glandular structures that when one of the pair undergoes destruction the other shows a compensatory hypertrophy. It is possible that this compensation will explain the occasional divergence between the anatomical conditions and what might be expected in case of disturbances in the excretory activity of the diseased glands.

To epitomise, it is evident that there is a certain number of conditions, more perhaps than we have at present recognised, in which we have auto-intoxication brought about by the disturbances in the internal secretory activity of various glands, or again by excess or diminution in the amount of the substances acted on by this internal secretion.

Disturbances of Growth and Nutrition.

These involve the consideration of the great broad process of metabolism, a process which is chiefly chemical. Metabolism must be viewed as both a local and a general process. Its results are three-fold, producing function, nutrition and new formation. The conditions for normal metabolism are :—

1, Normal blood and circulation.
2. Normal cells and cell medium.
3. Normal nervous influence.
4. Normal temperature.

When disturbances of nutrition occur we have either progressive or retrograde changes.

Progressive Disturbances or Productive Nutritive Disturbances.

These we consider under three main divisions.

First. Regenerative growths, *i. e.*, the replacement of lost tissue by a new growth of a similar nature.

Second. Hyperplastic growths, *i. e.*, the abnormal development of cells similar in character to those existing in the affected tissue, the new cells participating in the functions of the affected part.

Third. Tumours proper, *i. e.*, the abnormal development of cells, atypically and without definite limits, the new cells not participating as a rule in the functions of the affected tissue.

Regeneration.

The axiom for all regenerative processes is *omnis cellula e cellulâ*. The causes of the existence of regenerative power are found in increased nutrition, in certain chemical and nervous forces not well understood, and doubtless too in the inherent power of the cell itself to proliferate, *i. e.*, the vegetative power in cells

handed down from embryonal existence enabling them to reproduce their own kind. In other words the cell development is homologous. Heterologous cell development or metaplasia, which implies the formation of one kind of cell from some other different in type, does not occur as a rule. Epithelium gives rise to epithelium. Muscle gives rise to muscle tissue, etc., etc.

By far the commonest method of regeneration of tissue is that of Karyokinesis or mitosis. This process differs materially in different kinds of cells, and Hanseman has shown that certain types of mitoses are peculiar to certain types of cells; that, or example, the process in the epidermis is essentially different from that in the lymphocytes and endothelium, etc.

Regeneration may be both physiological and pathological.

Physiological regeneration is necessary to the anatomical completeness of the body and its perfect functional activity. Normally we have a balancing of cell production and cell waste; excess of production implies hypertrophy, diminished cell production induces atrophy or death, etc.

So far as physiological regeneration is concerned, we may divide tissues into three classes:—

1st. Those whose cells are constantly multiplying, *e. g.*, spleen, lymph glands, bone marrow, etc.

2nd. Those where mitosis occurs only around the period of birth, as in the liver and kidneys, *i. e.*, in the parenchyma of glandular organs with fluid secretions. In this class, too, must be included fibrous tissue.

3rd. Those where mitosis ends early in embryonic life, as seen in the striped muscles and nerves. Physiological regeneration in such tissues does not exist.

Pathological regeneration is found in all tissues, the type of cell formed differing according to the nature of the disturbance and the variety of tissue in which the process takes place.

REGENERATION OF BLOOD.—In hæmorrhages, the blood is replaced in adults in the bone marrow; in anæmic people generally one sees there the new red cells being formed, many of them nucleated. Occasionally in the severer forms of anæmia one sees

these new forming red cells in the circulating blood, indicating doubtless the marked attempts at regeneration. Normally nucleated red blood cells are found in the circulating blood only in the fœtus or at birth. Whether or not the red cells are formed thus entirely from the bone marrow is doubtful; probably for the most part they originate from the white cells.

White cells of the blood proliferate in the lymphatic tissue generally, as also in the blood, where mitosis and fragmentation can be readily observed.

REGENERATION OF EPITHELIUM.—This occurs by mitosis, and is always possible if some epithelial cell remain. Partial loss of epithelium is made up by new growths from the lower layers. In complete loss of epithelium, including the lower layers, the regeneration occurs from the epithelium at the sides. Destruction of the basement membrane and part of the substance of an organ results in a scar.

REGENERATION OF FIBROUS TISSUE.—Probably here the previously existing connective tissue is the main source of any new cells of the same kind. A participation of leucocytes in the new tissue formation is doubtful; at all events they play a minor role, and where regeneration occurs in connective tissue mitosis is most common and abundant in the fixed cells, much less so in the wandering cells or leucocytes. Grawitz's theory that slumbering cells exist in the matrix of connective tissue is given but little credence. According to this theory the fibrillar connective tissue would again become markedly cellular from the constant wakening up to activity and growth of cells which had previously disappeared, and remained latent awaiting the time for the need of regeneration.

Regeneration of *capillaries* occurs by the formation of little buds of protoplasm, originating doubtless from previously existing endothelial cells which have undergone mitosis. These buds lengthened out, become hollowed, and as they increase in size form loops which unite one with other, and thus give free passage and circulation to the newly entering blood stream.

REGENERATION OF CARTILAGE AND BONE.—When cartilage is fractured and reunited, bony formation is usually the result as in

the case of fracture of the costal cartilage. Often scar tissue or true cartilage may be the terminal stage in the repair of lesions of cartilaginous tissue. Lost bone is repaired by new bony tissue formation as seen in ordinary fractures. Provisional mitosis of the bony structures occurs giving rise to a periosteal callus, as likewise to a central or medullary callus ; later on a permanent regeneration of bone occurs in the intermediate portions giving us an interstitial callus, and then true bone. Complete functional activity of the bone may be obtained everywhere and the Haversian canals restored in perfection. The provisional tissue formed in the central and external portions is more or less gradually and completely absorbed. The growth depends entirely on the activity of the osteoblasts. Functional regeneration may occur without the morphological, as in a mal-united fracture.

REGENERATION OF STRIPED MUSCLE.—As a rule when striped muscle is cut, fibrous tissue is interposed in the repair, for the regenerative power of siriped muscle is very poor ; retraction of the fibres occurs and restitution at integrum is difficult. In febrile processes such as typhoid, where degeneration of muscle occurs, the repair is more perfect, because healthy muscle fibres usually exist amid those which have undergone waxy changes. In chronic diseases of the heart muscles with loss of tissue, repair usually occurs by the formation of connective tissues giving rise to interstitial myocarditis

REGENERATION OF NERVES.—The central nervous system has but little regenerative power. Ganglion cells when destroyed can never be replaced, but if the centre of the nerve cell with its nucleus be preserved one may get regeneration even though there be extensive destruction of the prolongations either centrally or peripherally. Conducting fibres are capable of regeneration ; they do not unite when cut as though by first intention, but the cells of the sheath of Schwann (neuroblasts) proliferate, the central part of their protoplasm becomes striated giving rise to the axis cylinder, and the medullary sheath forms secondarily around it ; this finally coalesces with the nerve stump giving us complete regeneration. Peripheral nerve fibres all die, the sheath of Schwann alone remaining.

Hypertrophy.

This implies over-growth or over-nutrition. Hypertrophy occurs in three ways.

1. Each cell in the tissue may be increased in size.
2. The cells may be increased numerically, *i. e.*, hyperplasia.
3. Both conditions may occur together.

Hypertrophy may be general or local. General hypertrophy is seen in giants and giant formations. Local hypertrophy may be physiological, as is seen in the pregnant uterus, the breasts and the enlarged prostate.

It may be pathological and as such is *congenital, developmental* or *acquired.*

Congenital hypertrophy is seen in the giant limbs at birth, as when an arm or hand or thumb are of enormous size as compared with the body elsewhere. (Riesenwuchs.) Ichthyosis is a congenital hypertrophy of the epidermis.

Developmental hypertrophy is exemplified in the epidermal horns seen most often about the face.

Acquired hypertrophy is due to various influences, increased nutrition and functitional activity, increased intermittent and recurring pressure or irritation, inflammation of a chronic type and sometimes diminished function.

Of the acquired hypertrophy due to *functional activity* increased work is the commonest form. The voluntary muscles of the body become thus enlarged provided that the work be not excessive and that the general nutrition of the body be maintained, *e. g.*, the biceps of the blacksmith. The heart in chronic valvular disease, more particularly in aortic lesions and in arterosclerosis. As examples of hypertrophy of unstriped muscles, we have the thickened bladder in stricture of the urethra, Increased functional activity causes hypertrophy of gland tissues also, more especially from compensatory needs. Defect of one kidney leads to compensatory hypertrophy of the other. Tubules, epithelium and glomeruli are all increased in size and

number. As a general rule it may be said that the more vigorous the tissue and the greater its developmental power, the better is compensatory hypertrophy accomplished. These are therefore best seen in embryonic life and early infancy.

Intermittent and recurring pressure as a cause of hypertrophy is seen in the ordinary clavus or corn, in the horny hands of the proletariat, and in the milk spots on the heart.

Chronic irritation as of chemieal, toxic or similar conditions produces hypertrophy, *e. g.*, condylomata in specific disease, the mucosa of the stomach in alcoholism. Chronic inflammation acts similarly, causing, for example, in the skin about inflamed parts a great increase in the number of epidermal cells.

Diminished function sometimes causes hypertrophy. The teeth of rodents elongate when not duly ground down by use, as when the corresponding teeth on the opposite jaw are absent.

Tumours Proper.

DEFINITION.—A tumour or neoplasm is the name applied to new formed tissue growing atypically both as regards form and limitations, and participating in no way in the functions of the body; *i.e.*, proliferating independently and usually without regard to the requirements of the organism.

The elements of a tumour, however, are always similar to those normally existing. They may be (*a*) homologous, *i.e.*, growing amid tissues containing the same elements as constitute the tissues of the tumour itself, or (*b*) heterologous, *i.e.*, composed of tissue elements differing from those already existing in the part from which the tumour arises.

The nutrition of tumours occurs similarly to other tissues in the body, some branch from a neighboring blood vessel carrying the blood to the neoplasm. In one sense, however, tumours are independent because they can remain well nourished while neighboring tissues are atrophied to a marked degree. Capillaries form the main vascular supply, the arteries and veins being in much smaller numbers.

Nerve elements are likewise found in most tumours, particularly the vasomotor nerves as evidenced by the rapid flushing of many tumours.

The growth of tumours may be rapid or slow according to varied conditions; sometimes a tumour long quiescent may take on a suddenly rapid growth, *e.g.*, by the removal of some obstacle to growth as the pressure of fascia on a tumour, or, as in many cases of Fungus Duræ Matris, where the overlying dura impedes growth until it is itself penetrated and the progress may then be very rapid. Again trauma or pregnancy or other conditions may be associated with the sudden lighting up of renewed rapid growth. Spontaneous healing of a tumour is extremely rare.

Neoplasms usually increase by a growth of new tissu within themselves, and as they grow their relations to surrounding struc-

tures differ. Circumscribed tumours, particularly when encapsulated, produce chiefly mechanical effects, and their gravity depends chiefly upon their situation, *e.g.*, a small tumour on the Clivus Blumenbachii may readily be fatal by pressure upon vital parts, while the same kind of neoplasm in the subcutaneous tissue may grow to enormous size without in any way affecting the general health. Other tumours tend more to invade surrounding tissues and are less circumscribed, and with these are associated definite characters. Hence the (clinical) classification of tumours into:

1. Benign or innocent.
2. Malignant.

Benign tumours consist of normal adult tissue, they grow slowly, are usually encapsulated, do not infiltrate surrounding structures nor do they invade the glands. Upon removal there is generally no local recurrence, the effects are purely mechanical and the general health is unimpaired.

Malignant tumours consist of unusual types of tissue either in the arrangement of the cells atypically or of the cells themselves. They grow rapidly and are not encapsulated as a rule; they invade all or any tissue and tend at the same time to destroy them. They form secondary deposits locally or in distant parts of the body. When removed they tend to recur and are either difficult to cure or ultimately fatal. They impair the general health and nutrition, tending to produce a condition of cachexia. This cachexia is due not to the fact that cancer for example is primarily a general disease, but because the metabolism in such tumours is enormous owing to the rapid destruction and building up of tissue within them, quite irrespective of any increase in the size of the growth.

It must be remembered that one cannot always make hard and fast lines between benign and malignant tumours inasmuch as there are numerous transition stages.

RETROGRADE CHANGES IN TUMOURS.—The tissue of tumours can show similar degenerative changes to those occurring in normal tissues. Degeneration is more common in the rapidly growing varieties. The more common changes are the results of

circulatory disturbances, mainly doubtless because capillaries are so prominent in the vascular system of neoplasms and because the relation of arteries and veins to the size of the tumour is extremely irregular. Hence, œdema, hæmorrhages, necrosis, calcification, pigmentation. In addition we get fatty and mucoid and colloid changes and coagulation necrosis. Cysts are often formed thus secondarily. All varieties of inflammation both simple and infective may develop in tumour formations.

Origin and Cause of Neoplasms.

Why do cells proliferate thus atypically? The causes are evidently not identical in every case (*vide antea* for the causes of hypertrophy). Sometimes injuries precede tumour formations, *e.g.*, fractures induce chondromata, blows on the breast precede mammary adenomata, etc. Sometimes chronic irritations are antecedent factors, *e.g.*, prolonged use of the clay pipe in cancer of the lip, the association of scars with epithelioma and of ulcers of the stomach with gastric cancer. The majority of tumours are not of infective origin, for their elements possess very little similarity to those produced in known infective conditions. Some neoplasms are undoubtedly congenital, while others again appear very soon after birth. All these are merely associated conditions of tumour formations and do not explain the actual cause.

Cohnheim's theory: This is based on the hypothesis that in early fœtal development more cells are formed in some tissue than are necessary to its anatomical completeness, or else that cells already formed become misplaced. In either case the superfluous cells remain quiescent for the time and perhaps for a long period thereafter, not tending to grow. So soon however as a stimulus arises development occurs and a tumour is formed. This theory is of course incapable of proof, inasmach as we cannot prove the existence of such cells. Roux however found in the frog's embryo in a number of instances misplaced cells, and showed on further investigation that the same could be produced artificially; this he thought should support Cohnheim's theory. It still remains to be proven however what is the further development of such cells and

whether they are capable of retaining the power of proliferation for any length of time. His theory seems plausible ; at all events for certains forms of tumours,—as for example in the case of dermoid cysts of the ovary which consist of skin, hair, teeth, etc., originating obviously from cells which became misplaced in fœtal life and remained quiescent till the stimulus for growth presented itself. Cartilaginous tumours of the parotid gland come in the same category. On the other hand, Cohnheim's theory cannot explain the origin of cancers.

Thoma explains tumours under two subdivisions, First, those originating according to Cohnheim's theory, Second, those due to external causes such as trauma, infection, etc., and adds to both of these conditions the predisposition of cell growth under various conditions.

Ribbert's theory makes no distinction of intrauterine and extrauterine process in tumour formations. No tumours grow he asserts from accessory livers, spleen or thyroids, and yet these are obviously misplaced germ cells. When an organ or tissue has attained full size, all its elements are in a kind of mutual tension, that is, cells are held together by the sum of all the mutual influences of the portions of the organ, one on the other. Any deviation of one portion which will tend to upset these mutual influences may cause irregularity of growth in one or other portion ; where the proliferative power is greatest a tumour may form, and where the energy for growth be small or the surrounding resistance too great, degeneration may result instead of new formation. The chief point in this theory is the ignoring of the embryonic idea in favor of the view that the organic combination of the cells in a tissue are necesary for its completeness and for the prevention of tumour formation. Ribbert holds therefore that tumours regenerate before and after birth because of the partial or complete separation of cells or cell groups from an organised combination of cells. The germ cells thus separated off may grow, and so long as they have enough proliferative power and nutrition they become independent and may form tumours ; according to the structure of the germinal tissue they may resemble more or less the organ from which they originate.

RECURRENCE AND METASTASES.—Some tumours possess the property of spreading to other parts of the body and inducing there a growth similar to the primary one ; in other words, a primary tumour can produce elsewhere in the body, secondary growths or metastases. These secondary deposits follow as a rule some definite system, as for example, the lymph or the blood circulation. The elements forming the secondary deposits are of the same nature as those contituting the primary focus. Metastases may travel by the blood stream (hæmatogenous) and may then give rise to thrombi or emboli ; in such cases where emboli exist one usually sees multiple tumours throughout the body mostly of the same size. Besides the ordinary malignant tumours sarcoma and carcinoma, one sometimes gets hæmatogenous metastases with enchondromata and myomata. Metastases again may spread from the lymphatic channels and in such cases involve also the neighboring glands. These travel usually in the course of the lymph stream, but when the lymph vessels are plugged they may pass backwards against the stream to other parts (*e g.*, involvement of the left supraclavicular gland in cancer of the stomach). Recurrence of tumours may take place locally when after removal some cells are still left behind. Complete removal of malignant growths is difficult inasmuch as individual cells may be carried rapidly to distant parts without leaving a trace behind them, even while the neoplasm is of recent origin.

Connective Tissue Tumours.

We must distinguish between histioid and organoid tumour. In the former but one type of cell exists in the growth, while in the latter there are several.

Connective tissue arises from the mesoblast. Not only does this portion of the mesoblast form tumours, but so also do other forms of tissue from the same origin, *e. g.*, bone, cartilage, muscle, etc. These can form growths each individually, or combined with one another or with connective tissue.

Fibrous connective tissue is the commonest of all to proliferate, as exemplified in all chronic inflammations, in the replacement of losses of tissue substance, etc.

In connective tissue tumours we must differentiate the various forms of connective tissue histologically, *e. g.*, the fibrillar, the areolar, the reticular, the mucoid, the fatty, and also the connective tissue of the nervous system, namely, the neuroglia. Various parts of the same tumour may contain each, all, or any of these various types, and according as the one or other variety of connective tissue predominates in the formation of an independent growth, so is the tumour named ; thus we speak of fibroma, myxoma, lipoma, glioma, etc. Sarcomata likewise belong to the class of connective tissue tumours, though the connective tissue here is in a state of arrested development.

Fibromata.

Classification.—These are classified in various ways. According to the *density* of structure, we speak of fibroma durum (hard fibroma), and fibroma molle (soft fibroma). Again, according to the *amount of blood* we speak of the teleangiectatic and of cavernous fibroma. When much *serum* is present we speak of œdematous fibroma.

According to the *form* we describe them as nodular, tuberose and papillary. Lastly, when there is an *admixture* with other tissues, we speak of myofibroma, lipofibroma, etc., according to the constituent elements.

Fibromata arise chiefly from pre-existing connective tissue and mainly where that tissue exists in denser masses, *e. g.*, the periosteum, submucous tissue and the perineurium of the peripheral nerves.

Clinical Features.—The fibromata are usually well circumscribed, often with a nodular or lobulated surface; they grow slowly, and have all the characters of benign tumours. When forming beneath the skin they may push it forward giving a tuberose form, as seen in the molluscum fibrosum and the common wart. Beneath the mucous membrane they often tend to become papillary, and the papillæ may be short and simple or long and branching. Each papilla in such cases contains all the fibrous tissue groundwork, including the blood vessels, and is covered by the epithelium of the affected part. Such, for example, are the condylomata of syphilis, the villous growths in the bladder which from their vascularity are often the cause of severe hæmorrhages. In the papillary form, of course, we have the growth and development especially in one direction, as opposed to the tuberose where the development is equal from all sides. Further examples are the nasal and uterine polypi.

Retrograde changes occur in the fibromata as in all other tissues, more particularly cystic degeneration (notably in the breast and uterus), hæmorrhages, calcification, necrosis, etc.

MYXOMATA.

Myxomata are connective tissue tumours containing mucine (which has a jelly-like translucent homogeneous appearance), and few fibres with numbers of spindle or stellate cells with long protoplasmic processes. Myxomata differ from the loose fibromata mainly in the nature of intercellular substance. Pure myxomata are very rare; one generally gets transition forms, such as fibromyxoma or lipomyxoma or myxosarcoma, etc.

LIPOMATA.

These consist of circumscribed proliferations of fat. Diffuse infiltration of fat is called *lipomatosis*. We must recognize, too, an intermediate stage between general adipose conditions and the lipomata, *e.g.*, perirenal fat proliferation, mammary lipomatosis, etc.

Fatty tumours occur in one of two ways: either, true new formations of fatty tissue, or else some connective tissue growing moderately, takes up an unusual quantity of fat and becomes a tumour. A third though rare method is by the mere heaping up or infiltration of fat in one certain spot. New formation occurs either from the connective tissue or from mucoid tissue, chiefly where this transformation normally occurs, *e. g.*, subcutaneous, ıbserous, submucous or subsynovial tissues.

Clinical Features.—Their characters are essentially those of benign tumours. Lipomata consist of masses of fat with thin connective bands between them, and therefore they are usually lobulated, soft and yielding, though sometimes firm, when combined with much fibrous tissue. They are often encapsulated and frequently polypoid (cf. appendices epiploicæ); the smaller ones are sometimes very vascular.

Sometimes they are congenital, though chiefly appearing in mid-age and later on; they grow intermittently. They may attain to a huge size, one on record weighing 275 lbs. They are often multiple; Broca mentions one case with 2080 lbs. Lipomate are ften mixed, and do not as a rule tend to degenerate.

The main *degenerative* changes which occur, however, are cyst formations, calcification and ulceration, the latter often yielding very foul ulcers from the formation of fatty acids.

GLIOMATA.

These are tumours made up of localized overgrowths of neuroglia and blood vessels. Diffuse increase of neuroglia occurs in ependymitis, in multiple sclerosis and tabes.

Gliomata are found entirely in the central nervous system and those portions of the peripheral nervous system which are associated embryologically with the cerebral vesicles, namely, the retina, the optic nerve and the olfactory bulbs. In the *spinal cord*, chiefly the gray matter is involved, and lengthy tumours may thus be formed. Cystic softening may follow with pressure on the peripheral parts, hence the diseased condition known as syringomyelia. In the *brain*, they occur chiefly in the white

substance and the posterior part of the lateral ventricles. They are not usually well circumscribed, often resemble a diffuse hyperplasia of cerebral substance, though of a more bluish translucency, and generally softer and more vascular; they are often hæmorrhagic or may be dry and cheesy. When they soften we get cavities.

Microscopically, scattered nuclei with round or oval form are seen, and closely arranged fibres and vessels. The picture varies according to the number of cells;—many cells give a medullary glioma or gliosarcoma. Many blood vessels give teleangiectatic glioma. Admixture with mucoid tissue gives myxoglioma, and when lime salts are deposited we get psammo-glioma.

Clinical Characters.—They are mainly benign tumours, and grow slowly unless they become sarcomatous; they are usually solitary, and very rarely indeed do they form metastases; they may become of large size without creating much disturbance. Fatal results may follow either through hyperæmia with hæmorrhage or through pressure on the venæ Galeni or choroid plexus, giving internal hydrocephalus, general anæmia and death associated with intracranial pressure. We sometimes get multiple minute gliomata formed upon the ependyma.

ENCHONDROMATA.

When cartilage proliferates it generally forms a tumour, chiefly in the bony structures. The size varies greatly, many chondromata being enormous. The seats of election are mainly the long bones of the extremities, the hands and feet. Chondromata form most often at the junction of cartilage and bone and frequently ossify (exostosis cartilaginea). We sometimes get smaller tumours, often multiple, in cartilaginous tissue itself, *e. g.*, trachea and epiglottis, and these have been termed ecchondroses. Sometimes in the joint we get nodes from the edges of cartilage becoming free and giving "free joint bodies."

General rule.—The farther the bone is from the trunk, the greater its liability to present enchondromata.

Virchow distinguishes enchondromata as heterologous tumours, and ecchondroses as homologous—though this he did not strictly adhere to in all cases, as we frequently get chondromata from bones as result of unossified cartilaginous remains. Chondromata are likewise frequently found elsewhere—in the parotid gland, the submaxillary region and the testis.

Clinical Characters.—Chondromata are bluish, more or less translucent tumours of firm consistence, made up of one or other of the various forms of cartilage. They are lobulated, the lobules separated by fibrous tissue containing blood vessels. Pure chondromata are rare, the cartilage tissue being usually mixed with mucoid or sarcomatous tissue or with true bone. They are as a rule benign tumours, though sometimes metastases form, spreading chiefly along the venous system, giving secondary deposits in the lungs.

Degeneration is not uncommon, associated with hemorrhage, cysts, calcification, etc.

OSTEOMATA.

Proliferation of bone is very common, and it usually grows from the periosteum, more rarely from the marrow; it is common, too, in other tissues (metaplasia). True osteoma is the result of ossification of new formed connective tissue other than that of inflammatory origin, and it may have all the characters of normal bone.

Nomenclature.— We classify osteomata in various ways. According to density we have (*a*) *osteoma eburneum*, chiefly on the frontral bone, consisting of smooth growths with a wide base, well circumscribed, covered by periosteum and with little or no cancellous tissue. (*b*) *Osteoma spongiosum*, commonly about the knee; they are more prominent and irregular with abundant cancellous tissue. (*c*) Medullary osteoma, of a still softer form, often combined with sarcoma.

A diffuse deposit or really periosteal outgrowth of spongy bone, which often later on becomes sclerosed, is called an *osteophyte*.

According to the relative positions of the new growth and the bone itself, we employ various terms; thus,

We speak of *periostosis* where much of the periphery of the bone is surrounded by new bony tissue.

Hyperostosis where the whole bone is surrounded, *e. g.*, acromegaly and leontiasis ossea.

Exostosis is applied to the form growing out from the bone in localized areas, and having the more tumour-like form. These are commonest at the insertion of tendons, and at the junction of epiphysis and diaphysis.

The term *enostosis* is used of a bony tumour in the midst of a spongy mass, and *synostosis* to such conditions as where the vertebræ are bound together by bony growths.

All these conditions belong to the category of homologous bony tumours. But we also have heterologous or heteroplastic osteomata where the bony tissue is formed in a situation where normally no bone is ever found. Such, for example, are the rare osteomata of the cerebrum, lungs, etc. Further, the condition known as *myositis ossificans* is worthy of note, being also a heterologous bony formation, characterized by a generalized ossification of muscles in various parts of the body.

Clinical Features.—Pure osteomata are very benign tumours. They grow slowly, and their effects are purely mechanical. Heredity seems to play a part in their formation; so too does previous inflammation.

Not infrequently mixed forms occur, and then they are apt to assume the characters of malignancy *e. g.*, osteosarcomata.

ANGIOMATA.

Angiomata are tumours consisting of vessels: those made up of blood vessels are *hæmangiomata;* lymph vessel tumours are called *lymphangiomata.*

Hæmangiomata are very common, for new vessels form easily.

Classification.—We may classify these growths according to the nature of their constituent vessels, as for example tumor vasculosis arterialis, or tumor vasculosis venosa, or cavernosa, also capillaris. The simplest form consists of an abnormal number of vessels or a collection of vessels, abnormal in width, shape or course, and

occurring oftenest where clefts have been present in the fœtus, less commonly in other portions or tissues of the body. The commonest example is the nævus or birth mark.

The capillary or teleangiectatic form (*e.g.*, nævus) is either congenital or forms early in life, occurs near fissures or clefts, such as the facial or cervical. Some though congenital are not fissural, occurring on the skin and in the subcutaneous tissue, often in relation with nerves.

They are flat, usually superficial, not encapsulated, grow slowly as a rule, and tend to remain local. Sometimes they grow rapidly and become malignant; their chief danger is associated with hæmorrhage and thrombosis. They often are mixed tumours combined with fat, bone, fibrous tissue, sarcoma, etc. Histologically they consist of a true new growth of capillaries forming a mass of dilated and varicose vessels, fusiform or saccular, and between them there is a varying amount of interstitial tissue.

Cavernous Angiomata consist of cavities or sinuses lined by a definite endothelium and filled with blood. The commonest sites are the liver, spleen, kidneys, brain and orbital tissue; they are common in the aged, especially in women.

Those in the *liver* are single or multiple, usually beneath the capsule and of varying sizes. They have a fibrous tissue frame work and really replace liver tissue, and are therefore in one sense not true tumours. They are common in the atrophic liver of the aged (senile angioma); many of them elsewhere are truly congenital.

Ætiology.—Associated with mainly four conditions: congenital, neuropathic, senile and traumatic.

The new formation of capillaries depends upon two factors: 1, blood pressure in the capillaries; and 2, the condition and attitude of the tissues in the neighbourhood. Altered pressure occurs easily at the fœtal clefts.

LYMPHANGIOMATA.

These are congenital or acquired. The commonest examples of the acquired are *macroglossia* and *hygroma*. The acquired are found in the skin and in the mesentery, the ordinary elephantiasis or Barbadoes leg being the commonest.

MYOMATA.

These are tumours consisting of smooth or striped muscle.

Leiomyomata or tumours of smooth muscle are the commonest and most important. The simplest contain unstriped muscle, connective tissue and blood vessels, and according to the relative quantities of these we have soft, hard and vascular varieties. The commonest sites are the uterus and the prostate. They are often multiple, and rarely form before adult life in the white races; they may attain a very large size, some on record weighing 70 lbs.; they are usually combined with fibrous tissue as fibromyomata, and the cut surface of such tumours presents greyish glistening bands of fibrous tissue, while the muscular part has a more dull grey red colour. One often sees a large vessel centrally, hence the theory of their vascular origin.

Microscopically their nuclei are less oval than those of sarcomata, more regularly together in bands, and thinner and longer; one usually sees but few blood vessels and many mast cells.

Chemically the muscle resists strong acids, while the fibrous tissue is dissolved in caustic potash in a short time.

We classify *uterine myomata* according to the situation, as subserous, submucous and intramural. The first two are often pediculated, and the pedicle may be thin and often twisted (thus giving rise to circulatory disturbance within the tumour); sometimes it may break, setting the tumour free in the abdomen or in the cavity of the uterus.

In the *prostate* they cause enlargement of the gland and encroach on the urethra, producing various vesical disturbances. Leiomyomata are also sometimes found in the stomach, the skin, the small intestines and the veins; in all these cases being homologous; they occur rarely in the pleura (heteroplastic).

Clinically they present all the characters of benign tumours, and cause disturbance mainly by their mechanical effects.

The ætiology is thought to be associated with either congenital or irritative disturbances.

Rhabdomyomata or tumours of striped muscle.—These are very rare, are oftenest congenital or occur in infants. The commonest

situations are the heart, kidneys, female genitals and testes. They are often associated with sarcomata, and occur frequently where no muscle normally exists.

SARCOMATA.

Sarcomata are tumours of the connective tissue type. The cells differ from ordinary connective tissue in that they remain in the stage of arrested development; they are essentially cellular tumours, the cells predominating over the stroma. They arise always from connective tissue elements.

From the fact that their constituent cells exist as incomplete fibrous tissue, one may expect the various developmental forms of cells to be present. We therefore get sarcomata with round cells, with small and large spindle cells, with irregularly shaped cells, and often with those which are multinuclear. Sometimes one or other form of cell will predominate, giving to the tumour certain characteristics from which it derives its special name, *e. g.*, round cell sarcoma, etc.

Sarcomata do not consist purely of cells but possess a very fine connective tissue stroma; they are therefore really complex tumours consisting of an insignificant stroma and a parenchyma (the cells), which gives to the tumours their characteristic features. The stroma is commonly very vascular. Where it and the parenchyma are morphologically similar, it is hard to detect their relationship, as in the fibrosarcomata; where, however, the two are more or less unlike, as in angiosarcomata or osteosarcomata, the relations are more distinct and more easily seen.

Sarcomata are distinguished microscopically from fibromata by various features, *e. g.*, their cells are in a stage of arrested development; there is less intercellular substance and less fibrillæ, and therefore the nuclei appear much more closely together, *i. e.*, the growth is more cellular; transition forms of course exist, giving us fibrosarcomata. The blood vessels of sarcomata vary in number; sometimes the cells of the tumour form the only visible walls of such vessels; lymphatics do not seem to exist.

All forms of *retrograde* changes may occur in sarcomata, such as fatty, mucoid, putrefactive, hæmorrhagic, ulcerative, etc.

Clinically, sarcomata belong to the most malignant forms of tumours, recurring on removal and often giving early and very general metastases; sometimes, however, they are peculiarly benign, as, for example, in the epulis, the tumours of the salivary glands and the giant cell sarcomata. Being mainly associated with blood vessels, the blood circulation is the commonest channel of transmission, and therefore secondary nodules appear, particularly in the lungs. Sarcomata may produce marked cachexia; the blood suffers chiefly by a loss of the red cells, the white on the other hand being often increased in number. They are essentially tumours of early and middle life.

Classification.—They may be classified under four heads:—

1. Simple, *i. e.*, tumours with connective tissue cells whose development is arrested and which have a fairly even distribution of the cells without any special groupings.

(*a*) Small round celled sarcoma,
(*b*) Large round celled sarcoma,
(*c*) Small spindle celled sarcoma,
(*d*) Large spindle celled sarcoma,
(*e*) Giant cell sarcoma.

2. Alveolar, where the cells have a special grouping or arrangement in or around vessels, giving to them a semblance of epithelial tumours, *e. g.*,

(*a*) Alveolar sarcomata,
(*b*) Angiosarcomata,
(*c*) Cylindromata,
(*d*) Myxosarcomata, etc.

3. Degenerative forms, where secondary degenerative changes occur in the cells, the matrix or the vessels, *e. g.*,

(*a*) Melanotic sarcomata,
(*b*) Chloromata,
(*c*) Sarcomata,
(*d*) Myxomatodes,
(*e*) Psammomata, etc.

4. Mixed forms of tumours, *e. g.*, fibrosarcomata, osteosarcomata, etc.

Small Round Cell Sarcomata.—These occur mainly in the extremities, in the skin, ovaries, testes and lymph glands. They are soft tumours and grow rapidly as a rule. Macroscopically, the cut surface has a milky-white appearance with perhaps caseation in parts, and in scraping over with a knife, one gets a milky juice; microscopically, small cells and vessels are seen; the cells are round, with relatively large, round or oval nuclei surrounded by but little protoplasm; between the cells there are very little granular fibrillar substance and thin walled vessels.

Lymphosarcomata resemble the gland tissue, the stroma being made up of tissue with anastomosing branched cells. Microscopically they resemble the round cell forms; they occur mostly in the glands and adenoid tissue of mucous membranes.

Large Round Cell Sarcomata are either simple or alveolar; they resemble the small round cell form, though much firmer; they are found in similar situations. The cells are larger with more protoplasm and a larger vesicular, more or less oval nucleus. When alveolar, the tumour is divided into smaller areas by coarse and fine septa, which, too, often penetrate between the individual cells, resembling carcinomata.

Spindle Cell Sarcomata have both large and small forms, they are very common, usually firm but sometimes soft, translucent and with a grey-white surface. The fibres run in all directions, and the amount of nuclei (oat shaped) and intercellular substance varies. The nuclei fill up well the bodies of the cells, the latter usually lying closely packed together. The small cell variety is more often encapsulated than any other form, though sometimes apt to infiltrate and to recur. The large spindle forms are softer, degenerate easily, grow rapidly and are extremely malignant.

Giant Cell Sarcomata (*myeloid*).—These are made up mainly of spindle cells, among which are interspersed many multinuclear cells with irregular outlines resembling cells from the bone marrow. The giant cells are not derived from the bone marrow, however, but are accidental rather than essential, and due to the action of foreign agents. (All cells may become giant cells when substances which are absorbed with difficulty are brought into contact

with them, because this leads to rapid nuclear division.) Possibly, too, they are sometimes formed from capillaries or from a fusion of degenerated cells.

Clinical Features.—Giant cell sarcomata are commonest at the ends of the long bones, *e. g.*, humerus, femur or jaw; they may be myelogenous or periosteal in origin. If they grow from the marrow, the compact bone "expands" and we then get the "egg shell crackling" due really to formation of new thin bone from the periosteum and to absorption of the old bone (bony tissue is, of course, incapable of expansion). The periosteal variety is commonly seen in the jaw (epulis). Giant cell sarcomata are often firm though sometimes gelatinous and of a reddish colour from hæmorrhage; they rarely form in later life, and belong to the least malignant of sarcomata; they are often encapsulated by the periosteum.

Alveolar sarcomata have definite histologically-combined structure, and the structure often depends on the origin. They are most commonly associated with vessels (either blood or lymph), and may grow from the endothelium or the adventitia.

We hence classify *hæmangio-sarcomata* into two varieties, the intravascular and the perivascular. Such tumours have usually a rich vascular supply; they consist of strands of cells with but little intercellular substance arranged in and around the vessels and following them. They occur in the brain, kidneys, testes, mammary glands and bones.

The *lymphangio-sarcomata* are mainly of the intravascular variety, and are seen most commonly in the serous sacs and in the membranes of the central nervous system. The angiosarcomata are very subject to degeneration, particularly mucoid and hyaline, giving us one form of the myxosarcoma and the cylindromata,

Cylindromata.—These are related to the myxosarcomata, though their exact nature is ill understood. They present microscopically a network of trabeculæ made up of cells, and enclosing cells and globules which have a distinctly hyaline appearance. These hyaline bodies may appear as spheres or in cylinders with projections on all sides (resembling a cactus plant). Within, one

sometimes sees cells with angular projections, like those of mucoid tissue, and likewise the centre seems frequently made up of some small vessel with its endothelial lining, and the condition then seems to be one of degeneration of the adventitia of the vessel. The characteristic gelatinous material which is found in cylindromata probably arises in two ways—either intracellular, *i. e.*, the hyaline substance is deposited in the vacuoles of cells, or else the cells excrete the substance.

Degeneration Forms of Sarcoma.—

Melanotic sarcomata present in many of their cells dark pigment granules of a sepia tint which does not seem to originate from the blood according to elementary analysis, but seems to arise from a specific change in the metabolism of the cell itself. They arise chiefly in the skin (especially over the parotid and foot), from nævi, also in the choroid of the eye and the iris. They are extremely malignant, the extension being not so much local as general, by the blood stream. The secondary deposits may have much more pigment than the original growth, and the pigment may further extend to the cells of the organs in which the metastases are deposited. They are often alveolar and perivascular, and in such cases the pigment exists in the fibrillated septa as well as in the cells.

Chloroma is the name given to a form of sarcoma (chiefly of the round celled variety) whose tissues when exposed to light become distinctly green in colour. This event is probably due to the presence of globules of a fatty nature, soluble in alcohol, and which at all events give the micro-chemical reaction of fat.

Psammomata are tumours containing special concretions. They are commonest as sarcomata, though one finds the benign tumours similarly affected. They occur as sarcomata mainly in the nervous system (the pineal gland, meninges, and choroid plexus), and present concentric bodies resembling the corpora amylacea seen elsewhere. They are allied in a measure to the cylindromata. The concretions often seem to supervene upon hyaline and mucoid degeneration.

Cancer.

DEFINITION.—Cancer may be described as a neoplasm of a malignant type derived from epi- or hypoblastic cells.

According to this definition, under the heading of Cancer we include both those tumours developed from squamous epithelium and from acinous glands. This is the usual acceptation of the term ; some, however, limit the term cancer purely to the malignant new growths derived from acinous glands.

CHARACTERS OF CANCEROUS GROWTHS.

These are best understood if we suppose that the cancer begins first as a local proliferation of the cells in a gland follicle. From being typical the cells in the course of proliferation become rounded and of more imperfect type ; from forming a single layer they form several, and now the proliferated cells burst through the basement membrane of the gland, and still proliferating extend along the lymph spaces. Just as all epithelia and cell-forming gland follicles are normally extravascular, so these proliferated cells remain extravascular and gain their nourishment from vessels in the surrounding stroma, or connective tissue. Hence the cancer is always of the organoid type, and consists of (*a*) altered glandular or epithelial cells lying in (*b*) a supporting and nourishing meshwork of connective tissue. These two elements are always present in a cancer. It will be seen that the method of extension is thus mainly by lymph spaces and lymph vessels as opposed to the more frequent extension by the blood vessels seen in the sarcomata. This, however, is not the only method of extension ; we can in fact recognize the following methods :

A. LYMPHATIC EXTENSION.

(1) Direct extension along lymph spaces and lymph vessels with secondary growths in the nearest lymph glands.

(2) Growth either in continuity, or by carriage of individual cells, in a direction opposite to the ordinary lymph flow, *e.g.*, after

cancer of the breast with involvement of the axillary glands, the head of the humerus may become cancerous.

(3) Contact growth along the lymphatics of a neighbouring organ by contiguity. Example, cancer of the liver or diaphragm secondary to cancer of the stomach without adhesion between the organs, such cancer apparently being brought about by passage of free cancer cells from the surface of the primary growths into the superficial lymphatics of the organ.

(4) Extension by grafting. It is difficult to know how exactly to classify these, because all secondary cancerous nodules may be regarded as grafts. There are, however, cases of superficial grafting that can be mentioned, *e.g.*, development of nodules upon mucosa of stomach secondary to cancer of epithelium of mouth, or of superficial cancer of inner side of arm secondary to ulcerative cancer of mammary glands. Such grafts must be regarded as extending along lymph spaces.

B. Extension by the Blood Vascular System.

Cancerous processes invading walls of veins, the cancer cells being carried to other organs, *e.g.*, cancer of stomach is not infrequently followed by secondary nodules along the branches of the portal vein in the liver, and in mammary cancer several cases have been recorded in which the femur has been found cancerous.

Classification of Cancer.

Cancer may be divided into (1) epithelial cancers developed from squamous epithelia — Epitheliomata, and (2) the glandular cancers — Carcinomata proper — developed from definitely glandular structures.

This second group may be divided into (1) *round cell* cancers and (2) the *columnar cell* cancers or *adeno-carcinomata.*

These different forms may be again divided according to the relative portion of connective tissue stroma and of cancer cells in the alveoli into (*a*) *scirrhous* cancer, in which the dense stroma predominates, (*b*) *encephaloid* or *medullary*, in which the alveoli are large and the cells greatly in excess of the stroma, and (*c*)

carcinoma simplex, in which there is no manifest predominance in either element.

(1) EPITHELIOMATA.—It is unnecessary here to go into the clinical or the histological features of the epitheliomata. In general they cause rapid affection of the nearest lymphatic glands with much ulceration and local destruction of tissue. Most frequent seats: the lower lip, tongue, tonsils, skin of hands, of legs, labia, penis and œsophagus. These arise most frequently from the Malpighian layer of the skin or from the hair follicles, more rarely are cases found which appear to rise from the sebaceous glands of the skin.

(2) ROUND CELL CANCER.—Most frequent seats: mammary glands, stomach, upper portion of the intestines, liver, pancreas, uterus, etc. These are more liable to form more distant metastasis than do the epitheliomata. And here in this we most frequently see the development of the tendency towards the scirrhous type of tumour.

(3) The COLUMNAR CELL CANCER, seen most frequently in connection with the rectum and lower portion of alimentary canal, though other cases of adenocarcinoma are to be seen in connection with the ovary, the bile ducts or the large ducts of the mammary glands, etc. The intestinal forms are more especially liable to manifest mucoid and colloid degeneration.

ÆTIOLOGY.

The following are the most important factors:

AGE.—Cancer is especially a disease associated with the period of beginning atrophic changes in the tissues, while sarcoma more especially shows itself at the period of active cellular multiplication. Cancer thus is a disease of middle and advanced age, sarcoma more especially of youth.

SEX.—The frequency of cancer in connection with the organs of generation makes cancer more common in the female sex than in the male, the female generative organs undergoing greater changes.

HEREDITY.

According to Paget one-third of all cases of cancer give a family history of the disease. It is difficult to make sure that this is the case; difficult, that is, to have absolute evidence that previous members of the family died of what was truly cancer. Undoubtedly, in some cases several members of one generation died from cancer, that is to say, there is a definite predisposition to the condition, but absolute proof is still wanting that heredity in the strictest sense plays any marked part in the development of the condition. Indeed it has been pointed out that one-third of the whole population must have a cancerous parent, grandparent or great grandparent. Where there appears to be hereditary tendency, it is to be noticed that the heredity is of the predisposition rather than of special organ affected. Thus cancer in the breast in the mother may be followed by cancer of the womb, etc., in the daughter. Another point at the present time which is liable to introduce difficulties into the discussion of heredity is the progressive increase in the number of cases of the disease. In 1840, in England, cancer caused 2,786 deaths, or one death in every 5,646 of the population. In 1894 the number of deaths from cancer was 21,422, or one in 1403 of total population. In other words, cases of cancer would seem four times more frequent, and this increase in frequency is apt to vitiate or to disturb our calculations, for the more we study the more it seems evident that the increased frequency is closely allied to the greatly lessened mortality from other conditions, especially from tuberculosis and the infectious diseases. Now the duration of life in England is several years longer than it was 50 years ago, *i.e.*, a large proportion of individuals who previously would have succumbed to other diseases live to be old enough to be affected with cancer.

MALIGNANCY.

Cancers vary in their malignancy; thus, for example, cancer of the tongue is usually very rapid, while cancer of the upper part of the face (*rodent ulcer*) is very slow. The one may cause death in a year from its first detection, and the other may be evident for

years. In general it may be laid down that the more cellular and the more vascular the cancer the greater its tendency to be malignant.

Theories as to the Causation of Cancer.

The theories as to the causation of cancer are very numerous; the following are perhaps the chief:—

(1) Diathetic. According to this theory there is an innate constitutional tendency to aberrant and excessive growth of one or other set of cells which does not show itself so long as the individual is in fair health, but some traumatic or other influence determines the active overgrowth. In other words, there is from the first some fundamental disturbance or want of balance of cell metabolism.

(2) The Histological or Embryonal Theory. According to this theory there is from the first an imperfect and atypical development of the tissue in which the cancer ultimately appears.

It is laid down in the terms of this theory that in tissues which have apparently arrived at maturity, a certain number of undeveloped cells still remain. From these residual embryonic cells later in life from the action of some unknown stimulus, cancer originates. Groups of such undeveloped cells forming *rests* may, by becoming displaced during development and included among adjacent tissues, be the starting point of heterologous or heterotopic tumours.

(3) Parasitic. The parasitic theory: that cancer is due to infection of the tissue by cancer organisms, that in short cancer is an infective neoplasm.

Let us consider the parasitic theory. Several observers, from Nepvu in 1872 onwards, have fancied that they have found bacteria in cancer, but have never been able to confirm their observations; no one now believes in the bacterial development of cancer. At present the majority of those favouring this theory believe that they can detect psorosperms in the cancer cells, while others, like Roncali, explain the appearance seen in the growing edges of certain cancers as due to presence of pathogenic blastomycetes or yeasts.

PSOROSPERMS (*coccidia* and *sporozoa*). The sporozoa are certain very low forms of animal life possessing the following features: that from the spore is developed an amœboid active little organism which in the majority of cases makes its way into some cell, grows in this cell, becomes globular and quiescent and in some cases becomes provided with a cyst wall and then divides up either directly or indirectly into a series of spores; the cyst breaks, these are liberated and under favourable conditions give origin to amœbæ. This is the typical cycle. The following species have been recognised among the sporozoa.

(*a*) GREGARINIDÆ. These are the largest forms of all, and are found parasitic in lobsters, cockroaches and other arthropods.

(*b*) COCCIDIÆ are intracellular parasites; best example, the *coccicidium oviformis* of the rabbit which is to be found very frequently in the cells of the intestinal mucosa and of the epithelium of the bile ducts. This shows a like series of stages, grows within the cells, forms cysts there; contents of the cysts divide into four and each of these four portions gives rise to elongated spores. An interesting fact is that this intracellular growth leads to great proliferation of the bile ducts and the production of local adenomatous nodules in the liver.

(*c*) MYXOSPORIDIÆ are forms of which little is known, forming amœboid masses in tissues.

(*d*) SARCO-SPORIDIÆ, parasitic forms found growing within the muscle sheaths of a great number of vertebræ. In the heart muscle, for example, of the ox, goat and sheep and other muscles of the pig, elongated plasmodia are found, often spoken of as Rainey's corpuscles after the old English veterinarian who first described them. This likewise, as pointed out by Hessling, forms falciform or crescentic spores.

(*e*) MICROSPORIDIÆ have been described by Balbiani in silk worms forming little masses within the cells of the intestinal epithelium, which masses eventually present a sporulation stage. These appear to be closely allied to the hæmatozoa of malaria.

(*f*) HÆMATOZOA. It is but necessary to call to mind here that the hæmatozoa apparently show the same cycle of amœboid resting and sporulating stages.

Now a great number of observers, from Darier, Thoma and Albarrin in the late '80s, have described forms both in cancer and in precancerous stages, as for example in Paget's disease of the nipple, which appears to resemble stages in a like history of this nature. Space forbids that I should describe each of these in turn, but very full accounts have been given by Sjöbring, Metchnikoff, Podwyssozki, Ruffer, Sawtschenko, Korotneff and Sudakewitch. It is, however, fairly well agreed now that many of the forms at first described, more especially in epitheliomata, are of the nature of keratinous degenerations of the cells. And with regard to the other forms it has been pointed out by Danna, that the true sporozoa have chitinous envelopes which have special staining reactions, and that nothing corresponding to these staining reactions can be seen in cancers. This alone is sufficient to gravely weaken the theory. Add to this that Domergue and others have shown that the forms so far described can be explained as stages of cell degeneration. The blastomycete theory of Roncali and other Italian observers is to say the least improbable, because forms very similar to those pictured by these observers are to be found in cases of chronic inflammation wholly apart from cancer. We thus at the present time cannot regard parasites as the cause of cancer. The question is, how far are the other theories capable of explaining matters?

While it is true we come occasionally upon certain examples of primary cancer of bone, etc., it can only be explained as originating from some inclusion of epithelial tissues in the growing bone. Cohnheim's theory is incapable of explaining all cases of cancer or malignant growth. So large a number of cancer cases give a history of direct relationship between the growth and previous irritation of the part that we shall have to assume the peculiar frequent presence of these abnormal cell rests. We should have to suppose that scattered throughout the body of every individual there are numerous cell inclusions of this nature, and that it is a matter of chance whether one of these be injured and cancer develop or no. There is, however, this to be said, that the cells of a cancer do present an embryonic appearance; that in

chronic inflammation we have a tendency for the cells to assume such embryonic appearance. It is not necessary with Cohnheim to suppose that the cells in a cancer are attaining a condition beyond which they have never advanced ; we can equally well suppose that a cancer may have developed from an adult tissue which from chronic inflammation or other cause has reverted to an embryonic condition. Here it appears to me is a more likely solution of the difficulty. We must suppose that cancer and other tumours are due to disturbance in the life history of the cells of a given part, whereby these cells assume more embryonic characters and take on the habit of growth independently of the needs of the issues.

Cysts.

Besides the blastomata or neomata, or tumours proper, it is common to include among the tumours two other classes of formation, namely, cystic and dermoid growths.

Cystic growths are difficult to classify, they are so extremely diverse in origin and in characters. We may, however, recognise the following forms:—

1. Retention cysts.
2. Serous, bursal and synovial cysts.
3. Necrotic or absorption cysts.
4. Parasitic cysts.
5. Cysts of developmental origin, tubulo cysts.
6. Dermoid cysts derived from epithelial inclusions.

RETENTION CYSTS.—These have so frequently been mentioned in the practical course that there is very little need to say much here. Remember that all glands produce their excretion with a certain amount of pressure, *i.e.*, place a manometer in the duct of the gland and the mercury will rise in the further limb of the tube to a considerable extent before the excretion from the gland is stopped. Thus any obstruction in the course of the duct of a gland is followed by pressure behind the point of obstruction, distention of the lumen of the gland, flattening of the epithelium, formation of cyst.

Such retention cysts may contain clear fluid, or there may be gradual absorption or transfusion of fluid, inspissation and condensation of the more solid constituents of the excretion so that the cyst contains thick, more or less crystalline material. Such retention cysts may be (*a*) small in the course of the individual gland follicles, or (*b*) may be large, affecting the whole gland where the main duct is blocked, *e.g.*, hydronephrosis of kidney following blocking of ureter, hydrometra due to contracted os uteri, imperforate hymen, etc.

Cyst-adenomata are also to be included among retention cysts, there being no outlets for the secretion of the neoplastic gland

tissue, *e. g.*, cystadenoma of mammary gland and ovary and thyroid.

Apparently closely allied to these retention cysts are the multiple *congenital cysts* of the kidney and liver, occasionally met with and apparently due to some obstruction or inflammation during fœtal life. Closely allied also to retention cysts may be mentioned *hæm-* and *lymph- angiomata*, in which, through pressure of the lymph or blood and weakness of the vascular wall, blood and lymph cysts are produced.

SEROUS CYSTS.—The serous cysts are apparently allied to the retention cysts. Normally, it need scarcely be said, there are present in the connective and other tissues abundant lymph spaces with free circulation of the lymph through these. In some cases of chronic irritation the flow of lymph appears to be increased, the absorption and passage off to be diminished, and so accumulations of fluid may develop either in pre-existing serous cavities, as for example in the synovial cavities, or again between layers of connective tissue, in which latter case bursæ develop, *e.g.*, housemaid's knee from much kneeling and washerwoman's elbow.

Intimately connected with these serous cysts must be mentioned cysts developing in connection with peritoneal diverticula, notably the different forms of hydrocele, cysts of the canal of Nuck and cystic enlargements of hernial sacs. While again, another class that may be brought in here is the whole collection of cystic enlargements in connection with either the central canal or the membrane of the brain and spinal cord—hydrocephalus internus, meningocele, syringo-myelocele and spina bifida.

ABSORPTION OR NECROTIC CYSTS.—These are well seen as developed after the so-called cerebral apoplexy. Where there is hæmorrhage into the brain substance the broken down brain tissue is replaced eventually by clear serum and a thin wall cyst is thus developed. Similar cysts of hæmorrhagic origin are to be found, as pointed out recently by Dr. Bradley, in the thyroid, more especially secondary to adenomatous conditions of this gland. Simple necrotic cysts not infrequently develop in tumours, espe-

cially where they are large, and the more central portion of the tumour has its blood supply cut off with resulting necrosis.

PARASITIC CYSTS.—There are a few parasites, nematodes and tæniæ which in one or other stage of their development produce sacs more or less distended with fluid in which the main portion of the body lies, the sac itself being part of the body wall of the parasites. Outside this there is frequently a developed boundary wall of connective tissue, a reaction on the part of the tissue of the host. The largest of such cysts is the hydatid cyst, formed by the *tænia echinococcus* which is most common in the liver but has been found single or multiple in almost every organ, including the heart muscle and the eye. *Cysticercus cellulosæ*, the cause of measly pork, affects man also, and like the hydatid is found in most various tissues. Compared with the previous form it is minute, and usually it only sets up slight disturbances even in the brain. It does not always give rise to disturbances. The *trichina spiralis* is minute, and the capsules or cysts formed by it lying in the striated muscles of man and animal are just visible to the naked eye.

CYSTS OF DEVELOPMENTAL ORIGIN.—These cysts form a most important group. In the process of development there are several passages and connections between organs and the exterior, or between different organs which normally close up and are completely absorbed. Occasionally the absorption is incomplete, and sooner or later the epithelial lining of these passages excretes fluid, distends the passages and a cyst or cysts are the result. Examples: the bronchial clefts passing between the pharynx and the side of the neck may persist to a greater or less extent, and according as to whether the persisting part is originally developed from the surface or from the pharyngeal epithelium, do we hear of cysts having a squamous epithelial lining, or those which are ciliated. Remains of the post-anal gut probably furnish many of the cystic glandular tumours of the coccygeal origin, while remain of the urachus, Wolffian and Muller's ducts give rise to cysts in connection with the bladder, broad ligament, vagina and testes.

DERMOID CYSTS.—The last mentioned cysts may all be placed as dermoid cysts, they all have an epithelial lining and are of developmental origin. There are other dermoid cysts of a slightly different nature which must here be mentioned, the so-called *implantation cysts*. These are to be seen more especially upon the extremities and upon the sclerotic and iris of the eye. If after operation a portion of the skin be stitched in, it sometimes happens that this abnormally placed portion continues to develop, becomes eventually globular with a central cavity, and thus a little cyst is formed of epithelial structure but of traumatic origin.

Dermoids.

Under this title are grouped together a number of diverse growths which contain epithelial elements, and which occur in such situations where such epithelial elements are not normal. The majority of these are congenital ; some, however, are acquired. They vary from simple plate-like overgrowths of epiblastic tissue to most complex masses of irregularly connected amd useless combinations of almost every tissue in the body. Beginning with the simplest forms, we can recognise the following varieties :

1. IMPLANTATION DERMOIDS.—These are more especially to be found upon the limbs where dermoids otherwise are not to be found, in the subcutaneous tissue there and elsewhere, and growing in connection with the cornea and iris. These are due to trauma. Some portion of epithelium becoming planted in a deeper tissue, continues to grow, and most commonly gradually develops into a small globular and cystic body.

2. CONGENITAL SIMPLE IMPLANTATION DERMOIDS.—During the course of development detached or sequestered portions of surface epithelium may gain attachment and growth elsewhere, chiefly in places where during embryonic life coalescence takes place between the epithelial surfaces. These may be found along mid-dorsal or the mid-ventral line, in the region of the branchial clefts, etc. They are usually cystic, and may contain hair and sebum : more rarely they are solid. Allied to these are some of the congenital dermoids found on the cornua and sclerotic, consisting of islets of skin bearing hairs. Boyce quotes a case in which the peritoneum was sprinkled over with miliary hair-bearing patches.

3. OVARIAN DERMOIDS.—The simplest are cysts lined by stratified epithelium, others simply contain hair and sebaceous follicles; a great number present well-formed teeth and bone, sweat glands, nipples, gland substance, brain matter and various reminiscences of fœtal tissues. Such ovarian dermoids it is

difficult to explain. Some would hold them to be of congenital origin, and to be inclusions of some rudimentary undeveloped embryo; but the fact that not infrequently dermoids of this nature may develop from both ovaries is strongly against such a view, as is the very great rareness of the cases in which these ovarian dermoids have been discovered in childhood. Others, and perhaps the majority, hold them to be of the nature of prathenogenetic growths, the aberrant developments of some unfertilised ovum of the individual in whom they are found. We know so little about the matter that it is unsafe to agree with any present view.

4. TERATOMATA; or dermoids derived from the rudiments of an included and twin embryo. One may have every stage of the development of a twin embryo, from the condition of identical twins through a stage like that of the Siamese Twins, where the two embryos remain united and perfect save for the union, down to a small polypoid projection most often at the caudal extremity of the body. In the ova of certain animals two or more embryos may by chance develop from the one ovum. Most frequently one of the two has a very vigorous growth, and the other undergoes more or less shrinkage until finally it remains as a mere cellular appendage to the other. Where the two embryos remain in part united union is most frequent at the lower end of the vertebral column.

These Teratomata may be of all forms, simple fatty or cystic, or bony, or granular, etc. On the other hand they may present well developed limbs and portions of the body springing from or attached to regions of their "host."

The General Pathology of the Blood.

The condition of the blood, its composition and the variation in the circulation of the same, of so much importance to the body as a whole and so profound an influence on the various tissues that in a course of general pathology the study of this fluid is absolutely necessary. It will be seen immediately that we can group our subject into:

1. Alterations in the amount and composition of the blood.
2. Alterations in the circulation and distribution of the blood.

Alteration in amount may be either in the nature of excess of blood—Hyperæmia—or diminution in the quantity—Anæmia. Both the hyperæmia and the anæmia may be (*a*) local or (*b*) general.

Alterations in the composition may affect:

1. The plasma of the blood.
2. The red corpuscles.
3. The white corpuscles.
4. Other elements.

Hyperæmia.

General Hyperæmia.—There has been much debate as to whether the condition of general hyperæmia or plethora really exists. On the whole it must be admitted that while on the one hand we have evidence of the presence of mechanisms whereby the quantity of the blood in a given animal tends to be preserved at one constant amount, we also have evidence that the amount of blood in different individuals varies very considerably. If we attempt to estimate the exact amount of blood obtainable from lower animals, we find that this varies between 1-10 and 1-16 of the body weight, and in the post-mortem theatre it seems obvious that some individuals are full blooded, others the reverse. It is obvious further, from the enlarged hypertrophied hearts of

those drinking large quantities of fluid, that there is something rather more than a temporary increase in the amount of their blood. Thus the tendency is nowadays to acknowledge that there may be plethora, and on the other hand there is an unwillingness to describe any special series of morbid disturbance as a result of such plethora, save a possible hypertrophy and dilatation of the heart and possibly increased arterial tension.

If we consider the lymphatic circulation as part and parcel of the venus, we then can recognize one special form of plethora associated with increased pouring out of fluid into the lymph spaces with imperfect removal of the same, and return to the blood: the so-called hydræmic plethora. Such hydræmic plethora may be,—

1. More especially associated with artero-sclerotic disease and diminished secretion from kidneys. The blood is of a thinner quality, the water and salts poured out in increased quantities from the weakened capillary walls, and the body becomes water-logged.

2. Again a very similar condition of water-logging is to be seen in general venous congestion in which fluid venous circulation and increased pressure in capillaries and veins and imperfect oxygenation of the blood, also in increased pouring out of fluid into the tissues.

LOCAL HYPERÆMIA.—This may be due to (*a*) increased passage of blood into the part from the arteries—Active Hyperæmia. (*b*) To diminished outflow of blood from a part—Passive Congestion or Passive Hyperæmia.

ACTIVE HYPERÆMIA.—Remember that this may be physiological, as during increased activity of glands and other tissues, or be pathological, such pathological hyperæmia being most frequently seen in the early stages of inflammation; or again as a result of nervous disturbance; or thirdly, compensatory, as where one of a pair of organs has been destroyed and the other acts for both. There is little that need here be said as regards this active hyperæmia beyond that the dilatation of the arteries leads to increased

passage of blood into the part and increased nutrition of the part. Whether this increased nutrition, both under physiological and pathological conditions, leads to increased growth, is extremely doubtful. It would seem that increased work as well as increased nutrition are required to bring about such overgrowth. So also active hyperæmia alone appears very rarely to cause increased exudation. Remember that increased exudation is not from the arteries, but from the capillaries and small veins. It rather appears as though there must be something beyond increased blood flow and increased pressure to bring about any marked increase in the amount of exudation under these conditions.

PASSIVE HYPERÆMIA.—Any obstruction in the outflow of blood from a part brings about the condition of passive hyperæmia. Such may affect one organ alone, or, on the other hand, be very widespread as in cases of obstructive heart and lung disease, or again of obstruction of the portal circulation as in cirrhosis. The organ which is the seat of passive congestion is dark in colour, superficial veins dilated, abundant blood oozes on section, which is of a dark venous character, resulting from the removal of oxygen from blood which becomes remarkably venous. There is increased pressure in veins and capillaries due to obstruction, imperfect nutrition of tissues, more or less marked atrophy of tissue in consequence of (*a*) imperfect nutrition, (*b*) pressure. Increased pouring out of fluid from the blood, more marked in some tissues than in others. Capillary hæmorrhages in some tissues with deposit of blood pigment. Where the congestion is marked and of long continuance there is liability to fibroid changes. Where obstruction is complete there rarely develops necrosis and gangrene because of the, in general, abundant capillary venous circulation by which the blood can find other outlets through the area. Such necrosis and gangrene most often develops as the result of local obstruction of the nature of constriction, *e.g.*, incarcerated hernia, where the pressure is sufficient to arrest the venous outflow from the part without arresting the arterial inflow.

Anæmia.

(*an* without *haima* blood.)

The term anæmia is unsatisfactory from an etymological stand-point. When there is any loss of blood there is an evident effort to add fluid to the blood, and so bring it up to its normal amount; thus true *quantitative* lack of blood would seem a rare and in general a temporary condition. What we have to deal with is thus a *qualitative* change, a thinning and altering of the constituents of the blood. Remembering this, we can continue to employ the term anæmia, or if we like we can employ the term oligæmia (which indicates "poverty of the blood," and is, in consequence, more strictly correct). Such anæmia or oligæmia may be *general* or *local*.

General Anæmia or Oligæmia.

Causes—1. Loss of blood, *e.g.*, by hæmorrhage, menorrhœa, intestinal worms.

2. Deficient formation of the constituents of the blood, as from insufficient food, dyspepsia, want of sunlight, etc.

3. Excessive drain and removal of substances from the blood, as brought about by excessive secretion of various kinds, lactation, albuminuria, etc.

4. Acute diseases lead in some cases to actual destruction of blood elements by the toxic substances elaborated, in other instances act more especially by rapid drain.

In all these cases, according to the process especially at work, we shall note the following features more or less characteristic of the altered blood.

Loss of red corpuscles, and with them loss of hæmoglobin.

Low specific gravity of the blood and thinness of the same, the blood becoming increasingly fluid and more or less hydræmic. For example, if there has been a severe hæmorrhage, the quantity

of the blood temporarily is greatly diminished ; rapidly there is poured into the vessels an increased amount of fluid from the lymph spaces, and indeed from the tissue cells, as Roy and Lazarus-Barlow pointed out. [After hæmorrhage the specific gravity of tissues and muscles increase ; this increase can only be explained by the fact that these cells have given up some of their fluid into the surrounding lymph.] This increased pouring out of fluid into the vessels is of course a dilution of the blood ; the number of corpuscles per cb. mm. is diminished ; the blood is thinner and more watery.

These may be said to be the general features of anæmic blood, but the more carefully we study the subject the more do we realize that the anæmias associated with different conditions vary among themselves. We can thus recognise clinically and to some extent pathologically the following forms of anæmia :

Post hæmorrhagic anæmia.
Progressive pernicious anæmia.
Chlorosis.
Hydræmia or serous anæmia.
General anæmia of chronic disease.

To these we may add certain conditions in which the leucocytes are more especially affected, the conditions of leuchæmia and pseudo-leuchæmia. It will be well to say a few words concerning the main features of these different forms.

POST-HÆMORRHAGIC ANÆMIA.—This is characterised by diminution in number of erythrocytes with corresponding diminution in amount of hæmoglobin and definite increase in the number of leucocytes.

PERNICIOUS ANÆMIA.—In this disease we have clinically a progressive weakness of the individual, which becomes very extreme without any marked objective or subjective symptoms beyond characteristic lemon-yellow coloration of skin and persistence of fat ; the patient in general is in a flabby condition. The exact cause is unknown. In the majority of cases there is found post mortem evidence of some lesion of the stomach and upper portion of the intestines of the nature of an atrophy or destruction of the

mucous membrane. An anæmia closely resembling this, if not identical, is produced by the action of some of the intestinal worms, notably the *Bothriocephalus latus* and the *Anchylostomum duodenale*. The disease is progressive, with frequently an intermission during which the patient appears to regain health and return towards the normal condition of health, only, however, to sink back into the anæmic condition and to die.

State of Blood.—The erythrocytes are diminished down to a million or in some extreme cases to half a million per cb. mm. They are characterised by great variety in size and shape (*poikilocytosis*), occasional but rare presence of nucleated red corpuscles; there is no extensive leucocytosis. *Diminution in hæmoglobin does not go hand in hand with a diminution in the number of red corpuscles*, or, in other words, the *amount of hæmoglobin per corpuscle is definitely increased.* Specific gravity diminished. An analysis by Dr. Ruttan has shown further a marked diminution in the serum globulins.

As to the meaning of this remarkable condition, observations in the post mortem room seem to throw some light; as above mentioned, there is most frequently atrophy or destruction of mucous membrane of the stomach and upper intestines. There is fatty degeneration of the various organs, especially of the heart and liver (such fatty degeneration is frequently associated with extreme anæmia and poverty of the blood). The red bone marrow of the bones and sternum is generally found increased, indicating the increased production of red corpuscles. Evidently, if there is such increased production to bring about the condition found in the blood, there must be very great destruction of the same corpuscles. As first pointed out by Quincke, the liver shows great increase in the amount of iron contained; instead of 0.07 p.c., there is upon an average 0.7 p.c., or about ten times as much as normal. This iron must have been taken up from the destroyed red corpuscles; we thus have abundant evidence of destruction of corpuscles and an increased formation of corpuscles. To explain this Hunter suggests that there is absorption of toxic substances through the diseased mucous membrane of the

alimentary canal, and these toxic substances lead to the breaking down of the red corpuscles. Broken down red corpuscles are taken up by the spleen and their products passed on to the liver, and there in part excreted as bile, the iron being retained.

Similar disturbances can be brought about by various products, notably by Toluylendiamene, and with these also there is a similar increase of iron in the liver. This at present is the most satisfactory explanation of the condition. The anæmia induced by the above mentioned intestinal worms may be due to a similar cause, as also the anæmia of pernicious type associated with ulcerative cancer of the stomach.

CHLOROSIS.—As the name implies it is characterised by a greenish tinge of the skin, the "green sickness" of old English writers; it affects mainly young females from the development of puberty until the 25th or 30th year. It is characterised by loss of activity, those affected becoming easily exhausted, while there is frequently obstinate constipation. The main character of the blood is that the *hæmoglobin is diminished far more than the number of corpuscles;* the corpuscles may be about 70 p.c. of the normal, while the hæmoglobinometric measurement may indicate only 40 p.c. to 45 p.c. of the normal; in other words, each individual erythrocyte has an impoverished supply of hæmoglobin. Autopsies can rarely be made, the disease not being in itself fatal, but in death from intercurrent disease it has been found frequently that there is a poorly developed arterial system, a fact to which Virchow first called attention. There are often imperfectly developed generative organs; this, however, is not always the case.

Causes of Chlorosis.—Very little can be said at all positively concerning this. It has been shown by Lloyd Jones that in all females with the development of the menstrual period there is a lowering of the specific gravity of the blood, due to the menstrual flow, and with this a lowering of the hæmoglobin per corpuscle. Thus the character of this chlorotic blood is but an exaggeration of this normal curve of blood change during young womanhood. This would indicate that the development of chlorosis is very closely allied to

and dependent upon the changes in the sexual life of the female due it may be to the greater drain upon the resources of the individual than that individual can easily stand. But this does not seem to clearly explain everything. There does not, for example, appear to be any close correspondence between variations in the menstrual functions, amenorrhœa, menorrhagia, etc., and variation in the chlorotic state; add to this that a very similar blood condition, a "male green sickness," have been recorded by several, and here in Montreal more especially by Dr. C. F. Martin. Such young male adults show all the symptoms characteristic of the chlorotic girl; the only point of difference is that the condition is not so extreme, and that the hæmoglobinometric estimation does not fall below 45 p.c., a point which is very frequently reached in the female. Add, also, that a like condition of blood is at times found in the female after this menopause. In a case which recently came to the post-mortem room (chronic alcoholism and pulmonary and intestine tuberculosis), two years after the menopause the blood showed erythrocytes, 4,800,000; leucocytes, 8,000; hæmoglobin 38 p.c. Thus other influences have been called upon to explain the condition, among them more especially chronic constipation. The absorption of toxic substances from the colon has been held by Sir Andrew Clarke and others to act as a blood destroyer, and so many observers from Hay of Aberdeen onwards have cured, or attempted to cure, chlorosis by the use of saline purgatives in addition to iron compounds.

It is well to note here that advanced chlorosis, clinically and hæmometrically, is at times very difficult to distinguish from pernicious anæmia. When the number of red corpuscles is greatly diminished, the amount of hæmoglobin per ce. becomes relatively greater. And, again, in such advanced chlorosis, poikilocytosis becomes very evident.

HYDRÆMIA OR SEROUS ANÆMIA.—This form of anæmia is found more especially in connection with chronic artero-sclerosis accompanied by renal disease. A close if not identical anæmia is to be found in obstructive heart disease and chronic exhaustive illnesses. So far there has been an inadequate study of

this form. Briefly, the blood is of low specific gravity, and there is diminution of the red corpuscles with no marked increase in white corpuscles. In all these cases there is a loss apparently of the circulating albumens of the blood and lowered nutritive quality of that fluid, with the result that not only are the general tissues of the body imperfectly nourished, but, whether from the specific substances circulating in the blood or from its mere poverty, the vessel walls would also seem to become affected ; in any case, this is to be noticed that these forms of anæmia are particularly liable to give rise to œdematous and dropsical conditions from the freer pouring out of fluid into the tissues which tend to become water-logged.

LEUCHÆMIA.—Before passing on to discuss this form of anæmia, it will be necessary to say some few words with regard to

LEUCOCYTOSIS OR HYPERLEUCOCYTOSIS,

and the modification in the number, both actual and relative, of leucocytes in the blood. The subject of leucocytosis has been much studied of recent years. Normally, as I have already pointed out when treating of inflammation, the number of leucocytes in the circulating blood is relatively small, being from 8,000 to 9,000 per cb.mm., as compared with the 5,000,000 erythrocytes. Normally, also, the polymorphonuclear (neutrophiles or finely granular oxyphiles) are the most frequent form, the lymphocytes the next, while the coarsely granular oxyphiles or eosinophiles are present only in minute proportions, 2 p.c. to 4 p.c. The finely granular oxyphiles average about 60 p.c., lymphocytes about 30 p.c. The other forms, namely, the hyaline and the finely granular basophile, are in minute numbers ; the coarsely granular basophiles are absent from the healthy blood.

The number of leucocytes present in the blood varies considerably within physiological limits ; thus the new-born animal has relatively abundant leucocytes during the first eighty hours of life (up to 19,000, mainly lymphocytes). In pregnancy there is a slight but definite increase to 12,000 or 13,000. After meals there is an increase of a few thousand, mainly in the lymphocytes and

finely granular oxyphiles or polymorphs, while the eosinphiles and hyaline diminish. On the other hand, with lack of food and starvation, the lymphocytes and neutrophiles or polymorphs diminish and the eosinphiles increase. Roughly, it may be said that, if the number of leucocytes be under 12,000, no marked leucocytosis can be spoken of, nor can we speak of *leucocytopenia* or *leucopenia* until the number is below 6,000.

Pathologically we may have similar increase or diminution in the number of leucocytes; thus, the mere tying down of an animal has been shown by Löwit to bring about a rapid diminution in its leucocytes; so, also, shock and shaking animals does the same, the hyalines and the polymorphs or neutrophiles being diminished. Whether this diminution is due to actual destruction of leucocytes or *leucolysis*, or whether it is due to an arrest of many of the same in certain capillary systems, is at present a matter of debate.

A similar diminution follows an injection of both chemical and bacterial poisons, more especially bodies such as ferments, pepton, leech extract, curare and bacterial toxines, while, as Sherrington has pointed out, acute local inflammation brings about a rapid diminution of the neutrophiles. In most of these cases the leucopenia is followed by increase in number of leucocytes, the increase being both in the lymphocytes and in the neutrophiles. The following forms of leucocytosis have been recognised :—

1. *Post-Hæmorrhagic.*—The red corpuscles may be diminished by hæmorrhage to 3,000,000 or so, but, with this diminution, the white corpuscles are found to have risen to 16,000 or more within twenty-four hours after the hæmorrhage. Gradually the number of the red corpuscles returns to the normal and the number of the white corpuscles diminishes.

2. *Premortal or Agonal.*—During the death agony, more especially where that is of some few hours duration, the number of leucocytes in the blood markedly increases, and may rise to as much as 50,000 or 60,000 where death is ushered in slowly. With this great increase in leucocytes may be pointed out the liability for the development of ante-mortem coagulation of the

blood in the heart and great vessels, more especially on the right side.

3. *Cachetic Leucocytosis.*—In progressive disease of various forms, more especially in cases of cancer and malignant tumours, there may be a great diminution in the number of red corpuscles associated with the corresponding increase in the leucocytes, generally the polymorphonuclear leucocytes, though in sarcomatous cases we may find a marked increase in the lymphocytes.

4. *Inflammatory and Infective Leucocytosis.*—The condition of the leucocytes and their number vary in different diseases, and, while it cannot be said that in all cases the study of the leucocytes at the present moment is able to help us, it must be acknowledged that in some instances the study of inflammatory leucocytosis has been found to be of signal diagnostic and prognostic value. This is notably the case, for example, in connection with acute croupous pneumonia, in which condition there may be an increase to about 23,000 per cb. mm. so that in a case of doubt as between pneumonia and typhoid (in which there is no marked leucocytosis), the enumeration of the leucocytes is most valuable. Add to this that it is found that, if a case of pneumonia is progressing favourably towards the crisis, there is a daily increase in the number of leucocytes. On the other hand, if it is progressing towards a fatal termination, there is a progressive and sometimes rapid decrease in the number of leucocytes seen in the blood.

Other diseases in which there is found a definite leucocytosis are cases of non-tubercular inflammation of the serous membranes, in diphtheria (up to 16,000), acute rheumatism (slight, up to 12,000), pyæmia (variable), erysipelas (often considerable), cholera (in the algid stage, the number increases to 40,000 or 60,000). In tuberculosis and malaria there is no marked leucocytosis, and if present it appears to be associated with secondary infection.

Thayer has recently shown that trichinosis may be diagnosed by the enormous increase in the number of eosinophilous leucocytes in the blood (up to 50 per cent. or more of the total

number) and a similar but not quite so great increase in the eosinophilous cells as has been pointed out in connection with pemphigus.

5. *Leuchæmia.*—This is a disease generally of a chronic nature characterized by the presence of relatively enormous numbers of leucocytes in the circulating blood. As a general and empirical rule or convention, we speak of *leucocytosis* when the number of leucocytes of the blood is below 50,000 per cb. mm.; of leuchæmia, when the number constantly exceeds this figure. The condition here noted was first recognized by Bennet, of Edinburgh, in 1845; he considered it as a pyæmic condition of the blood, and spoke of it as leucocythæmia. Within a few weeks, Virchow, of Berlin described the condition more fully, regarding it as due to some disturbance of the lymphatic apparatus, and named it leuchæmia. While Bennet has the priority, and while therefore his name ought to be employed, it must be admitted that leucocythæmia is a cumbrous word, so now generally we speak of leuchæmia.

It is evident from the numerous cases that have been reported and the studies that have been made that there is more than one affection which leads to an increase in white corpuscles of the blood. Two main conditions may be recognized: (1) in which the main anatomical change is the enormous increase in the size of the spleen, (2) in which the lymphatic glands throughout the body are enlarged. A sub-variety of the first has also been recognized, in which more especially the white marrow of the bones is increased in amount, so-called, *myelogenic*. Almost always this condition is associated with enlargement of the spleen, and indeed follows at a later stage of the splenic disease, so that perhaps it is best to speak of two main forms, the *lieno-myelogenous* and the *lymphatic*.

It is in the former that there is the greatest increase in the number of white cells, which may be found as many as 100,000 or even 250,000 per cb. mm., the proportion of white to red being 1:10, 1:5, or even 1:1. According to Osler, cases have been recorded in which the leucocytes undoubtedly out-numbered the red corpuscles. In one case at the Royal Victoria Hospital, the blood, after death

showed the white corpuscles greatly out-numbering the red. In lymphatic leuchæmia the increase is not so marked, and the proportion of 1:10 is rarely exceeded. While the great increase in the number of white corpuscles forms the main feature of the leuchæmic blood, it should be noticed that the number of the red corpuscles is diminished, and they present a certain amount of poiklocytosis; the amount of hæmoglobin also is markedly lessened. The blood coagulates slowly, and is of lower specific gravity than normal, and its alkalinity is diminished. In the two forms of the disease the alterations in the leucocytes differ in the splenic form; besides fine granular neutrophiles there are *numerous coarsely granular oxyphiles;* there are present also very large mononuclear hyaline cells which are spoken of as "Markzellen," marrow cells or myelocytes. These cells are generally supposed to be derived from the bone marrow, and Mosler in puncturing the sternum during life found large numbers of these cells in the bone marrow. However, it is very doubtful whether these necessarily originate in this region, for they have been found also in the blood in cases of skin disease and in uræmia. In addition to the above elements there have been found *coarsely granular basophile cells* (which have been noted in the blood only in this disease and in hereditary syphilis), and, further, *nucleated red corpuscles* have frequently been discovered. The number of lymphocytes varies.

In the the *lymphatic* form there is no such increase in the eosinophiles and nucleated red cells; the myelocytes or marrow cells are absent, but there is a *great increase in the number of lymphocytes.* Thus the two forms are markedly different. It should, however, be added that there are transitional or combined forms, and here the diagnosis is difficult.

Cause.—As to what is the cause of this disease we are at present ignorant. So far, while several observers have found bacteria, mostly streptococci, in the blood, it has been mainly in the late stages, and the results have been far from constant; and, further, the bacteria found might have been due to a secondary infection, for abscess formation and hæmorrhage are frequently observed during the course of the disease. On the other hand, the irregular pyrexia accompanying the disease is, to say the least, suspicious, and it is possible that both the splenic and lymphatic

forms may be found eventually to be of the nature of chronic infective processes especially affecting the blood.

While we thus have conditions of either a large spleen or of enlarged lymphatic glands associated with the presence of excess of leucocytes in the blood, so also may we have enlargement of the spleen, or enlargement of the lymphatic glands, chronic conditions in which the general symptoms closely resemble those of these two forms of leuchæmia, but in which there is a very slight leucocytosis, if any, the number of leucocytes not attaining the 50,000 previously mentioned. These conditions are known, the first as *Splenic Anæmia* (first described by Von Jaksch), the second as *Hodgkin's disease*, *lymphadenoma*, or *lympho-sarcoma* (all these being terms employed by different observers). It is, to say the least, doubtful as to whether there is any sharp definition between the leuchæmic and the non-leuchæmic conditions, or whether, as Dr. C. F. Martin and others have pointed out, these may not be modifications or different stages of one and the same disease or diseases, *i. e.*, one may have marked enlargement of the spleen with increase in its lymphoid elements without increase in the leucocytes in the blood, and similarly have marked overgrowth of the lymphoid tissue of the body in general without the development of the lymphocytosis. Some of the recent cases here in Montreal certainly have shown at times the appearance of a lymphatic leuchæmia, as later at other periods there has been sufficient decrease in the number of leucocytes in the blood to render it necessary to speak of cases as Hodgkin's disease.

Acute Leuchæmia.

While the lymphatic form is in general like the splenic a chronic disease, there have been not a few cases recorded recently of acute development of a leucocytosis so extensive that it can only be spoken of as acute leuchæmia. The leuchæmia here is of the lymphatic type, and in this case more especially does the infective nature of the disease seem very evident. Not only is there well-marked pyrexia, but there is an almost constant history either of some exposure to some low form of infection (*e. g.*, the patients have been employed upon drain works, etc.), or they have had previous ulcerative processes in the mouth or along the alimentary canal.

Thrombosis and Embolism.

THROMBOSIS.—By the term Thrombosis we understand the coagulation of the blood within the vessels. Under ordinary conditions throughout life, while the blood removed from the vessels will rapidly coagulate, so long as it is retained within the vessels there is no sign of any such process. The very numerous observations made upon this subject of the coagulation of the blood have shown that so long as the endothelium of the vessels is in a healthy condition and is intact, for so long will the blood not coagulate. Whether this is due to some "vital activity" on the part of the endothelium or no is very doubtful. We find, for example, that if blood be received into a perfectly bland fluid, *e. g.*, olive oil, it will float on this without coagulation, or, as Lister showed many years ago, if the blood of the jugular vein of an ox be removed within that vessel by double ligature, that same blood may be kept for very many hours in the vessel without showing a sign of coagulation; and indeed the vessel may be cut in two so as to form two living test tubes, and the blood be poured from one part into the other without coagulation. In such cases the endothelium is intact, and can scarcely be spoken of as being in a position to present much vital activity. It would seem thus that the coagulation of the blood follows much the same law as does the precipitation and deposit of crystaline substances; so long as there are no projecting points upon which the process may begin, for so long is coagulation arrested. If the endothelium be destroyed by disease or violence, or again if foreign substances, as, for example, a needle, be projected into the vessel, then upon this media or foreign substance coagulation will take place.

It is true that certain experiments of Wooldridge would seem to point out that spontaneous coagulation may occur in the blood in the absence of endothelial disease. Thus if a certain amount of extract of the thymus gland be injected into the circulation, the blood throughout the body will coagulate, but if a lesser amount be injected, it has been found that not coagulation, but increase in

transudation ensues. This would seem to indicate that the extract has an energetic action upon the vessel walls, so that even here it may be that the coagulation is preceded by an alteration in the endothelium.

A further subsidiary influence in the coagulation of blood within the vessels is the diminished rate of blood flow or retardation of the blood ; this, however, is not a direct cause of coagulation. It would seem that it is only when that retardation leads to lowered vitality of the endothelium through malnutrition, that coagulation of the blood will occur.

Nature of the Processes of Coagulation.

The more we study the subject of thrombosis, the more we are led to the conclusion that there is more than one process at work. If, for example, we ligature a vessel or arrest the blood flow in an aneurismal pouch, we obtain what is known as a mixed blood clot, soft and homogeneous, and examining this we have the well-known characteristic strands of fibrin, between the meshes of which lie red blood corpuscles. The process here is identical with what occurs in the coagulation of the blood removed from the body. This, however, is but one form. If, as was first done by Eberth and Schimmelbusch, we introduce a fine needle into a small vessel in which the flow is fairly rapid, and then examine under the microscope the results of this injury, as can be done in connection with the frog's mesentery, we see quite a different process. We recognise that besides the red and white corpuscles, the blood contains a third element, the blood platelets—bodies which are oval or pyriform, translucent and very much smaller than either form of corpuscle. They are non-nucleated, and possess no movement of their own. It is these little bodies which are seen to collect upon the needle or other foreign body in the first place, and collecting thus, they fuse together into a hyaline homogeneous mass to form what is known as a white thrombus. This mass gives all the micro-chemical reactions of fibrin, but is devoid of the familiar threadlike appearance. Under further modifications of experiments one may obtain what may be termed a true mixed thrombus, in which, besides these collected blood platelets, we can

recognise broken down white corpuscles from which proceed strands of fibrin, and in some cases the thrombus seems to be almost entirely composed of such broken down white corpuscles with scarcely any blood platelets; it would thus seem possible to have a white corpuscle thrombus. We can thus recognise at least three forms of thrombus:

1. The thready fibrin thrombus with admixture of red corpuscles generally known as mixed thrombus.

2. Pure white thrombus formed of hyaline fibrin derived from blood platelets.

3. Mixed white corpuscle and blood platelet thrombus showing admixture of hyaline and thready fibrin.

THE BLOOD PLATELETS.

There has been much debate as to the exact nature of the blood platelets; they are not recognisable in blood withdrawn under ordinary conditions, but with special precautions (vide some text-book of physiology) they can be preserved and studied in the extracted blood of healthy individuals. There are several theories as to their nature:

(1). That they are the small precipitated or suspended masses of fibrino plastic material floating dislodged in the blood.

(2). That they are derived from broken down white corpuscles.

(3). That they are derived from the broken down red corpuscles. The study of the not infrequent thrombi in the branches of the portal vein in the liver by Dr. Staples here in Montreal last year seems strongly to favor the third of these hypotheses, that is to say, in these small vessels we can see that one portion of a transverse or oblique section of the congested vessel shows well preserved and well defined red corpuscles; these give place to minute circular or oval colourless bodies which seem to be due to the breaking down of those red corpuscles, and these pass almost insensibly into perfectly hyaline and homogeneous white thrombi. Thoma has arrived at the same conclusion. It must not be thought, however, that the nature of these bodies is generally regarded as having been settled.

Thrombi developed by any of these methods, whether of coagulation proper or by conglutination of platelets, may present themselves in more than one form. They may be:

A. *Obliterating*, so as to completely obstruct the flow of blood from a part. Such are often seen in veins; or B, *Parietal* and attached to one side of the vessel or to the walls of an aneurism, and still permitting the flow of blood past them.

Classification of Thrombi according to the Method of Production.

Marantic Thrombosis.—This is seen in chronic exhaustive disease, after acute zymotic disease, or again after severe hæmorrhages. In all these conditions there is very weak heart action and impoverished condition of the blood, and the coagulation is most liable to take place where the blood flow is weakest and the blood itself poorest. Thus it is in the veins of the lower extremities and of the pelvis that we more especially meet with thrombi of this nature, and again in the right auricle. With these marantic thrombi may be mentioned also the thrombosis occurring in the puerperal period in the iliac and femoral veins, leading to the production of the so-called "white leg."

Thrombosis due to Disease of the Vascular Walls.—This occurs more especially in conditions of atheroma and of acute inflammation of endocardium, arteries (rare) or veins (more common). In connection with inflammation of the valves of the heart it is well seen, and there it leads to the production of the so-called vegetations and fibrinous tags attached to the edges of the valves.

Traumatic Thrombosis.—Seen in veins after venesection and in the arteries after amputation.

Thrombosis of Dilatation.—Seen in aneurisms and varicose veins.

Compression Thrombosis.—Brought about by pressure of tumours, aneurisms, etc. By arresting the flow through a part, thrombi form in the badly nourished small capillaries, and extend along the vessels in which the flow has been arrested. Here may

be included the thrombosis which follows the ligature of vessels. Such thrombosis starts from the region where, through ligature, the endothelium has been destroyed.

THROMBOSIS AROUND FOREIGN BODIES.—Examples: coagulation of blood occurring around particles of thrombi which have been dislodged from some other region; around a detached portion of an atheromatous vessel wall; around fat globules and cancer cells which have found their way into the circulation, and again around microbes, as in pyæmia.

EXTENT OF THE THROMBOTIC PROCESS.

Where an obliterating thrombus fills an artery, it extends up that artery until the first considerable branch or division of the artery occurs, and extends down to the point where through some branch collateral circulation is established. In the veins the extent largely depends upon the presence of valves; where valves are absent, as in the venous plexus of the bladder, the rectum and the pregnant uterus, the cranial sinuses and the cervical veins. the process gradually extends over a very large area in the direction against the blood current. The presence of valves appears to arrest processes at the point where these occur. Where there is a parietal thrombosis the free flow of blood over the surface of the thrombus arrests or slows the process of coagulation. Thus in the veins, if there be no large anastomosing branch, the clot may extend a long distance also in the direction of the blood current.

COURSE OF THROMBOSIS AND FATE OF THROMBI.

(1) If the thrombi be aseptic and sufficiently small, they become eventually absorbed. At the point of their attachment to the injured vessel wall the vasa vasorum become congested and show evidences of inflammation; leucocytes exude and bring about breaking down and absorption of the clot; or (2) they may become dislodged, as frequently happens with the vegetations upon inflamed valves, and may be carried along in the circulation, bringing about a condition of embolism. (3) If the thrombi be of larger size and be aseptic they tend to undergo organisation.

The stages of such organisation can be best well followed in vessels that have been ligatured, or which have had their endothelium destroyed. The stages are the following :—

a. Development of the thrombus ; as above mentioned, the mass grows until it occupies the artery up as far as its nearest large division.

b. Inflammation at the site of injury of the endothelium.

c. Invasion of leucocytes and partial absorption.

d. Passage into the mass of new formed vessels derived from the congested branches of the vasa vasorum.

e. Development of connective tissue cells in the immediate neighbourhood of these new-formed vessels.

f. Eventual replacement of the dead fibrinous mass by fully developed fibrous tissue.

During this latter stage the thrombus has undergone great shrinkage, and now in the relatively small thrombus certain of the new vessels may communicate with the blood in the main vessel both above and below the obstruction. The exact stages of this communication are not known, but in this way communication may be established anew through the obliterated vessel and the thrombus becomes "canalised."

(4) If the thrombus be septic, the microbes present in it through their enzymes break down the fibrin and render it semi-fluid. At the same time the products of the growth of the microbe may set up a profound irritation in the vessel wall and so the vessel wall becomes filled with a porridgy or fluid purulent mass, and this may easily become dislodged, and being carried into the nearest communicating vessels may be arrested in other organs, setting up multiple pyæmic emboli and abscesses.

There are one or two other changes still to be mentioned, namely, (5) Under certain conditions the thrombosed material does not undergo organisation, but as seen especially in certain of the veins, becomes necrotic and undergoes gradual infiltration with calcareous salts, thus forming phleboliths. (6) Another form of aseptic necrotic change is not infrequently seen in the ball or sessile thrombi which may develop in the heart, most often in the appendix of the right auricle, but also in any of the other cham-

bers of the heart in exhaustive disease. Instead of undergoing organisation, the central portion of these thrombi may gradually be replaced by bland fluid or semi-fluid material, so that on section the thrombus is found to be cystic, having a fibrinous wall with fluid contents.

Embolism.

By embolism we understand the blocking of a vessel by some foreign substances carried to the part in the blood stream and leading to the blocking of the vessel, because continued narrowing of that vessel prevents its being carried further. The substance causing such blocking is spoken of as an embolus. I have already mentioned some of the most frequent of these foreign substances which lead to embolism. The following is a fuller list :—

(1). The dislodged products of the coagulation of the blood, *e. g.*, cardiac vegetations, portions of septic thrombi, etc.

(2). Portions of diseased vessel walls, *e. g.*, portions of the diseased endothelium and calcareous matter from atheromatous ulcers of the heart valves and arterial walls.

3. Cells from malignant tumours either (*a*) affecting the great lymphatics and reaching the blood through the thoracic ducts, or (*b*) perforating the vessel walls.

4. Cells from an abscess perforating the vessel walls.

5. Leucocytes becoming impacted in the capillaries, as may occur in leuchæmia.

6. Vegetable and animal parasites, embryos of tape-worms, trichina spiralis, bacteria, *e. g.*, tubercle bacilli and pyogenic cocci, (These lead to capillary embolisms. It is doubtful whether these bacteria ever pass along the blood in such masses as to produce embolism even of the smallest capillaries; more probably one or more bacteria passing into a small capillary with slow blood flow multiply in situ and block the vessel.)

7. FAT EMBOLISM.—Fat embolism occurs more especially in connection with fractures of bone and severe injuries. It results from destruction of the fat cells in the fractured bone and its neighborhood. In the passage of fat globules into the lymphatics and veins from these vessels the fat is carried to the lungs and there causes obliteration of the pulmonary capillaries. Such fat embolism may occur either immediately after the injury through

the rupture of the fat cells of the marrow and surrounding tissue, or may occur after an interval of some few days as a result of the inflammatory breaking down and atrophy of the fat cells.

8. AIR EMBOLISM.—This occurs through the incision or rupture of the larger veins in the neighbourhood of the heart, most often the veins of the neck which are close to the outer air. In these veins, during the diastole of the ventricles, there is a negative pressure, and if they be exposed to the air, air is sucked into them and so to the right ventricle. This air is churned up into fine bubbles by the valves, and these fine bubbles from their constitution become arrested in the finer capillaries of the lungs, blocking them and leading not infrequently to death, though probably death is more often brought about by disturbances of the tricuspid and pulmonary valves by the accumulation in their neighbourhood of the frothed-up blood.

9. PIGMENTARY AND OTHER EMBOLI.—Cases have been recorded where substances accumulating in the blood have led to embolism. The most marked example of this is to be seen in some cases of malaria where the pigment from the broken down red corpuscles may accumulate in the capillaries of the brain and other organs. In some cases of caries it is stated that the lime salts from the absorbed bone may cause similar capillary emboli.

Collateral Circulation and Infarction.

If a vessel, whether artery or vein, be occluded, that occlusion leads as a rule to the development of a collateral circulation, and such development is the general rule; indeed the observations of Goldblum have demonstrated that the occlusion of an artery always leads to formation of the collateral circulation if there is no special obstruction to be overcome. When a vessel is blocked, the lateral branches have not only their own capillaries but also those of the ruptured arteries at their service, and so have an enlarged capillary area, and through this enlarged capillary area the blood finds a more easy flow with lessened resistance. And as it is one of the mechanical principles of the circulation that the blood flows most easily in those regions where there is lessened resistance, so does the blood from surrounding vessels find a more easy path along the capillaries of the area supplied by the blocked blood vessel, and in this way the circulation is re-established through these vessels and collateral circulation is set up.

INFARCTION.—Such collateral circulation is developed less easily in certain arterial regions than in others, thus for example the peripheral branches of :—

The splenic artery.
The renal artery.
Brain substance.
The superior mesenteric artery.
The retina.

All of them, instead of anastomosing freely, tend to divide and re-divide without joining in with the arteries of surrounding branches ; they form what Cohnheim termed "end" or "terminal arteries." The lack of anastomosis is rarely complete, is perhaps most complete in connection with the splenic arteries. In the kidney the interlobular arteries and arteriæ rectæ of the cortex have some connections with the capsular blood vessels, but these connections

are very slight. In the superior mesenteric artery also, if the main trunk be blocked there are anastomes of the cœlic axis and in the inferior mesenteric a teries. In the lung also there is a double blood supply, the main supply being by branches of the pulmonary artery, but along the bronchi are similar branches of the bronchial arteries coming from the aorta, and these are capable to an imperfect extent of establishing a collateral circulation. In other organs also there is some difficulty in establishing such collateral circulation, the branches of the coronary arteries of the heart are mainly terminal, as would also seem to be many of the finer arterioles of the skin.

In all these cases, therefore, if the branch of the artery be blocked, it may be some little time before a collateral circulation is established, and the tissues supplied by the blocked artery may have undergone serious change before it is possible for an adequate circulation and nourishment to be established. Whether this circulation is arterial, through anastomosis of finer arterial trunks, or is essentially capillary, through capillary anastomoses, is after all a minor point.

What happens in these cases depends, it would seem essential, upon the rate with which collateral circulation is established, and we may distinguish the following conditions:—

1. The rapid establishment of collateral circulation, as seen in the limbs and in most regions of the body; absence of any ill effects save in the nature of slight inflammatory disturbances immediately around the embolus in the blocked artery.

2. The development of collateral circulation before the tissue has undergone necrosis. This condition is well seen in the lung. When the blood begins to flow into the part, it finds the capillary walls so much modified by lack of oxygenation and nutrition that in the first place they are paralysed and become enormously distended; in the second place, they permit not only exudation of much fluid, but the actual passage out of red corpuscles (hæmorrhage per diapedesin), they in fact cause the production of the *red infarct*. If sections be made of such infarct, the outlines of the tissue can still be seen feebly stained, the alveoli and the tissue spaces are filled with red blood corpuscles;

but here, as the circulation improves and (save in very large infarcts) the tissue gradually becomes healthier, the extravasated blood is absorbed or otherwise thrown off, and the part eventually returns to the normal condition.

3. Another stage is to be seen more frequently in the spleen. Here with the blocking of the terminal artery, the part supplied by the artery is at first completely cut off from the circulation, and there is formed a white more or less wedged-shaped area, so-called white infarct, composed of tissue which has undergone coagulation necrosis, in consequence of arrested nutrition, but gradually the blood finds its way into the vessels and sinuses of the part, which becomes greatly distended, the blood extravasates and a large swollen area is developed standing out above the surface level, composed of necrosed tissue and blood both intra- and extra- vascular. Such a mass is a red infarct.

4. A fourth stage or condition is to be seen in the kidney. Here, in man at least, the arteries are perfect end arteries, and when one cortical artery is blocked there results a wedge-shaped area of necrosed and coagulated tissue, a white infarct, which does not pass on as in the previous case to be the seat of hæmorrhagic change. There is here permanently a condition of white infarction, although it is true the dead area tends to be surrounded by a zone of congestion and inflammation. This difference between the condition of the human spleen and kidney is rather against the view of Thoma and others, that the flooding of the infarctous area by the blood is simply a matter of collateral circulation, due to the arterial supply; it is more in favor of the regurgitation theory, *i.e.*, that the blood finds its way by regurgitation from the veins, because in the spleen there is a relatively high venous pressure; in the kidney, connected as it is with the vena cava, a relatively low venous pressure. It cannot be said that as yet any positive conclusion has been reached in this matter of the arterial vs. venous development of the red infarct.

Course of Infarct.

(*a*) As above stated, where collateral circulation is rapidly developed there is absorption of the extravasated blood and return to the normal condition.

(*b*) Where there has been necrosis and development of infarct proper, the dead material acts as an irritant, and in a simple aseptic case we have, (1) development of surrounding inflammatory zone; (2) passage in of leucocytes; (3) absorption of dead tissue; (4) passage in of new capillaries; (5) formation of connective tissue around them from fibro-blasts, and in this way a replacement of dead tissue by new connective tissue; (6) that new connective tissue contracts so that the infarct is eventually represented by a small puckered cicatrix.

(*c*) If the embolus is septic, necrosis is followed by a breaking down of the coagulated tissue by the bacterial products, multiplication of pathogenic microbes, invasion of leucocytes, their death, abscess formation, etc.

(1) *Development of infarct in the brain.* The necrosed tissue is surrounded by an inflammatory zone, there is abundant pouring in of leucocytes and abundant absorption of the dead hæmorrhagic tissue with relatively little connective tissue formation, so that as the absorption goes on it is replaced by pouring in of serum and a cyst is formed, provided always that the destruction of tissue has not been sufficient to bring about rapid death.

In the *stomach* and *intestines* necrosis along the area of one of the terminal branches of the mesenteric arteries is followed by digestion of the dead tissue and the intestinal contents, and the formation of what is known as a *round ulcer*, which is funnel shaped.

According to Rindfleisch, C. F. Martin and others, quite a large proportion of purpuric spots are of the nature of red infarcts, and, where there is any scurvy, we find an eruption and development of annular hæmorrhages around about the hair follicles. What we have to deal with is a central area of white infarct surrounded by a hæmorrhagic or red infarctous zone. In such cases the force of the circulation has been so feeble that with the blocking of the artery blood only pours into the periphery of the area, and has not the force to affect the centre.

In bone, infarctous areas are seen more especially in connection with tuberculosis and more especially towards the ends of the long bone. The affected area undergoes necrosis, the bone is not completely removed, because here, as in other conditions of tuberculosis, the disease is associated with vascular obstruction, hence a sequestrum is left.

Hæmorrhage.

HÆMORRHAGE is the passage of blood out of its natural channels. This blood may proceed from any portion of the vascular system, the heart, the arteries, the capillaries or the veins.

In general, rupture of a large vessel leads to abundant pouring out of blood either into the tissue or upon one of the surfaces of the body. The results of such pouring out of blood depend largely upon the amount lost. It is a matter of common knowledge that a few ounces may be taken from an adult without any marked disturbance beyond some giddiness, pallor and thirst. When more than two litres (5 lbs.) is lost in the human subject, death takes place suddenly. Between such sudden death and the slight disturbance already mentioned, there are various degrees of giddiness, tendency to syncope and symptoms of Cheyne-Stokes breathing and convulsions.

Hæmorrhage of small quantities of blood frequently repeated leads to another chain of symptoms, namely, to well-marked anæmia with all its attendant conditions.

Minute capillary hæmorrhages may be accompanied by no noticeable symptoms, though recent work shows us that the pouring out of blood into the tissue, even in small quantities, may lead to a sharp rise of temperature, due apparently to the breaking down of that blood and the liberation of the fibrin ferment and associated bodies.

FORMS OF HÆMORRHAGE.

We recognise two main forms, *per rhexin* or rupture and hæmorrhage *per diapedesin*. Hæmorrhage may be into 1) internal cavities, (2) infiltrating or parenchymatous, and (3) external. According to the position of the hæmorrhage, so do we have different names; thus, we may have among internal hæmorrhages, —Hæmothorax and Hæmopericardium, among the parenchymatous,—Cerebral Apoplexy, and we might also include the Pulmonary Apoplexy, though this is more external than parenchymatous.

EXTERNAL HÆMORRHAGES:

Epistaxis, from nose.
Hæmoptysis, from lungs.
Hæmatemesis, from stomach.
Melæna, from intestines.
Hæmaturia, from the renal organs.
Menorrhœa and Menorrhagia, from uterus.

As to the forms that the hæmorrhage may assume, we have to recognise the following:—

Ecchymosis and Petechiæ, minute, multiple, infiltrating, seen in purpura.

Hæmorrhagic suffusion or infiltration.

Hæmatoma, where the blood is poured into tissue to such an extent as to form a tumour.

CAUSES OF HÆMORRHAGE.

1. External mechanical, from ulceration, trauma, atmospheric pressure, etc.

2. Internal mechanical, increased blood pressure seen in the epistaxis of cardiac hypertrophy, or again in obstructive heart disease in the branches of the pulmonary artery, or in passive hyperæmia, as for example in cirrhosis of the liver and obstruction of the portal circulation.

3. Disease of vascular walls, as, for example, fatty degeneration of heart leading to rupture of the ventricle. Atheroma of arteries leading to aneurism and subsequent rupture, or in some cases direct rupture.

4. In the capillaries, as seen more especially in acute inflammatory and zymotic diseases, in the hæmorrhagic forms of small-pox, yellow fever, scarlatina, plague, etc.

In the blood diseases where the condition of the blood leads especially to malnutrition of the walls, in purpura and scurvy, and again in diseases of the walls brought about by toxic agents, such as H_2S, P.K.I., mineral acids, etc., etc.

5. Neuropathic hæmorrhages, seen most frequently in some cases of hysteria, from the gums, throat and lungs in some cases of hæmorrhagic perspiration, in the stigmatism of religious mania, etc.

ARREST OF HÆMORRHAGE.—The very loss of blood in hæmorrhage by lowering the pressure within the vessels helps to render the flow less and less, but in addition in cases where there is rupture of the vessel walls, the blood coagulates around the edges of the wound, and the thrombus thus formed either stops the flow or lessens it according to the size of the vessel. Remember that there are other auxiliary causes, notably, in arteries, the retraction of the inner walls within the sheath, causing marked narrowing of the lumen, also actual contraction of vessels. (This favors the stoppage of hæmorrhage where the rupture or cut is transverse, but it is harmful and leads to continuance of hæmorrhage where the rupture or break in the arterial wall is longitudinal.)

RESULTS OF HÆMORRHAGE.

Besides the general results already referred to, one has to consider the changes which occur in the effused blood; these changes are:

1. If there is much infiltration there is destruction of the tissue, by displacement and pressure upon the individual cells and fibres of the tissue, as is well seen in the brain and the lungs.

2. Absorption of the more fluid part of the extravasated blood, the hæmorrhage at first soft becomes firmer.

3. Later breaking up of fibrin and absorption of pigment and of corpuscles and tissue debris by leucocytes. The hæmoglobin of the red corpuscles dissolves out and may be precipitated in the tissue either in granular form as hæmatin or in crystals of hæmatoidin.

4. If the hæmorrhage be large, there is not to be absorption, but organization according to the well-known method; if still larger the whole is not organized, but the centre softens, and there is eventually developed a more or less colorless cyst.

HÆMOPHILIA.

In connection with hæmorrhage a few words may be said with regard to the curious condition known as hæmophilia, in which either spontaneously or from very slight injury uncontrol-

able bleeding may be set up. The condition presents several remarkable features, which it is somewhat difficult to explain; thus in the first place it is characteristically an inherited condition. In one or two families the condition has been traced back for more than two centuries and through seven generations. The transmission of the tendency is peculiar in that it passes through the female members of the family. These female members are not in general themselves "bleeders," nor do they present any liability to profuse hæmorrhage, either menstrual or during and after parturition, but their male offspring many of them show this tendency to bleed at the slightest provocation. Usually the tendency shows itself in early childhood, but in some cases bleeding may not be noticeable until early manhood. Often associated with the bleeding is a liability to affection of the joints with pain and swelling closely resembling acute rheumatism.

When we attempt to find an explanation of the condition, we discover that there are no marked changes in the vessels. Some have described changes in the capillaries and in the smaller vessels but many careful observers have obtained negative results. Again, the condition of the blood appears to be quite normal. As might be expected after a hæmorrhage it is found thin and watery, but at the beginning of an attack of bleeding it is found rich in corpuscles and hæmoglobin and shows no lack of power to coagulate. On the whole the hæmorrhage would seem to be of the nature of a capillary diapedesis, though nothing positive can be said in this respect. Recent observations would rather tend to show that the condition was largely a neurosis, for cases have been recorded in which injury to the trunk and limbs led to no hæmorrhage, whereas the slightest scratch or blow upon the neck or face have led to uncontrollable bleeding. Cases like this show clearly that the blood is not at fault, and as it is difficult to comprehend why the vascular walls should be diseased or defective over a large area of the body and perfectly healthy over another, we are led to the conclusion that the difference in the action of the vessels in the two parts must be largely a matter of nervous disturbance.

Local Anæmia.

Besides General Anæmia or Oligæmia, we may have a true local anæmia or absence of blood from one or other region of the body. The most frequent and clearly marked examples of such local anæmia are brought about by the action of the nervous system. There may either be reduction in the blood supply by the *direct* action of the *vaso-constrictors* of the vessels of that part, or again there may be *complementary* local anæmia owing to the action of the vaso-dilators of some other part whereby the blood is drawn into that part, and other parts are temporarily deprived of their blood supply. It is often difficult to see whether the blanching of the part is due to one or other of these factors. Experimentally we know that we can produce it in either way, namely, either by stimulation of the vaso-constrictors of the organ, or by stimulation of the vaso-dilators of some other organ. Concerning hysteric cases, local blanching is well marked and sharply defined, and can only be due to the vaso-constrictor action. In the majority of cases, however, a local anæmia appears to be complementary; it is especially well seen in conditions of *shock*, where the congestion of the abdominal organs through localisation of their vessels may be so great as to rapidly cause the cerebral circulation of the brain to become anæmic, with *syncope* as a result.

Other cases of such local anæmia are to be found in obstruction of the flow of blood to the part either by pressure from without, as by tumours, or by diminution of the lumen of the vessels of the part, from disease of the walls, or again from the presence of some obstruction within the vessel either due to coagulation of the blood or to the presence of foreign substances. Or, in other words, local anæmia may be classified as follows :

A. ACTIVE.

Example, local asphyxia of Raynaud's Disease, pallor in neuralgia, constriction of vessels of skin in the rigor of fevers ; toxic, due to ergot, tobacco and lead.

B. COMPLEMENTAL.

Shock and syncope.

C. PASSIVE.

(1) From within : thrombosis and embolism. (2) From disease of the arterial walls; example, endarteritis obliterans of syphilis, chronic phthisis and some forms of malignant growth, *e.g.*, epithelioma. (3) From without : pressure of tumours, aneurysms, etc.

EFFECTS OF LOCAL ANÆMIA.

These may here be briefly set down as in the first place diminished temperature of the part, and, in the second, loss of function, and, in the third place, degenerative and necrotic changes in the part according to the nature of the vessels. These changes will be more fully considered in discussing the subjects of Thrombosis and Embolism.

DROPSY AND ŒDEMA.

We have in common use several terms which imply the collection of abnormal quantities of serous fluid in the cavities and connective tissue spaces of the body. Thus, by *œdema* or *anasarca* we imply infiltration of this serous fluid into the parenchyma of organs and the general connective tissue of the body. By *dropsy* we mean a similar collection in the various cavities, and according to the cavity affected so do we have special terms for this dropsy. *Ascites*, or abdominal dropsy ; *hydrothorax*, dropsy of the thoracic cavity ; *hydropericardium*, dropsy of the pericardium ; *hydrocephalus, internus* and *externus*, internal and external dropsy of the brain ; *hydrocele*, dropsy of the scrotum ; *hydrarthrosis*, dropsy of the joints. In general use *anasarca* is a generalised dropsy and œdema ; *œdema* a localised infiltrating dropsy of a part.

Such fluid accumulating in the tissues and cavities may be due, it is evident, to several causes. In the first place, any such fluid must primarily be derived from the blood, and it must accumulate in what are larger or smaller lymph spaces. Thus, the

amount of fluid in the tissues and lymph spaces at any given moment must depend upon two main factors:

1. The amount of fluid pouring out from the vessels.

2. The rate of flow of the lymph out of the tissues back into the blood.

Other things remaining the same, either obstruction to the lymph flow from a given part, or increased transudation from the vessels, must lead to the accumulation of fluid in the part, to a dropsical condition, and we can recognize thus two main factors of dropsy, *lymphatic obstruction* and *increased transudation* from the vessels.

A. Dropsies due to Lymphatic Obstruction.

Among the Lymphatic Dropsies, we can recognize the following forms:

Chylous Ascites due to rupture of the abdominal lymphatics with or without obstruction to the lymphatic duct and main lymphatics. The abdominal cavity becomes filled with chylous lymph, containing abundant fat, etc., absorbed from the food.

2. Pseudo-Chylous Ascites due to obstruction of abdominal lymphatics by cancers, tuberculosis or other growth without rupture of the abdominal lymphatics. The peritoneal cavity becomes distended with an opalescent fluid devoid of fat resulting from the transudation of the chylous fluid minus its fatty and more solid constituents through the walls of the distended and obstructed lymphatics.

3. Œdema of one or other extremity due to pressure of new growth, especially cancer upon the lymphatics coming from that limb.

4. Lymphatic Elephantiasis generally of lower limbs and of scrotum, due most often to obstruction of the main lymphatics of the limb or part by adult filarial worms. The feature of such œdema induced by lymphatic obstruction is that it is of a more solid and dense type than that due to vascular disturbances. Such œdema due to lymphatic obstruction differs from ordinary

œdema in that it is associated with a tendency to an immense hypertrophy of the skin and subcutaneous tissues. In an early stage one finds dilated lymphatics and a fluid and cellular infiltration of the tissues. At a later stage, this cellular infiltration or proliferation gives place to the presence of increased connective tissue.

A somewhat similar form of infiltration is seen in myxœdema due to disease of the thyroid. What is the exact succession of changes causing this myxœdematous condition is not accurately known. The same is true of the condition of solid œdema or sclerema.

Dropsy due to Increased Transudation from the Vessels.

The process of transudation from the vessels must be dependent upon three factors :—

1. The condition of the vessel wall.
2. The blood pressure.
3. The condition of the blood.

These will in most cases interact the one upon the other. If for example we have a condition of venous obstruction, so that (*a*) the pressure in the veins is raised, (*b*) with this the blood becomes more venous, and (*c*), owing to the deficiency of oxygen the vessel walls of the capillaries and veins are badly nourished, while at the same time they are distended and thinned. All these then will interact in the production of the dropsy.

1. The Condition of the Vessel Wall.—There has been much debate as to whether the transudation of fluid through the vessel wall is an act of filtration or whether it is something more than this, and is largely dependent upon the condition of the cells lining the wall. This is not the place in which to discuss fully this most important matter, which, however, has an important bearing upon this subject of dropsy, because, were this act of transudation merely filtration, then we should find that the greater the blood pressure within the vessels the greater would be the transudation. Or, in other words, the condition of the

vessel walls would play scarce any part in the production of dropsy. The observations of Heidenhain more especially have indicated that there is a selective secretory activity on the part of the vessel walls, and he has shown that certain substances pass out into the lymph far more rapidly than any filtration could bring about. So that, for example, after the introduction of sugar to the blood, within a relatively short time the lymph may contain a greater percentage of this substance than does the circulating blood. A point clearly indicating some such power of the vessel wall in determining the amount of fluid that passes out of it is a fact that not infrequently we obtain hydrothorax limited to one side. The blood pressure and the condition of the blood must be the same on both sides; the only factor that can be at work must be a difference in the condition of the vessel walls on the two sides. Thus then we may take it for granted that at one time a vessel wall will allow an abundant exudation, at another time it will prevent this, and we have sufficient ground for proving that when the vessel walls are diseased or have lowered vitality, then more especially are they likely to permit increased excretion and the development of a dropsical condition. It may be noticed that the relatively thick arterial walls permit very little passage of fluid from them, and that dropsy and the transudation of fluid occurs mainly from the arteries and the finer veins, or, to epitomise, transudation of fluid occurs mainly from the capillaries and small veins, and is in part (it may be) a filtration in part governed by the condition of the vessel walls.

2. BLOOD PRESSURE.—It is a moot point also whether the blood pressure as such has a direct influence upon the transudation of fluid, for under physiological circumstances the blood pressure may be very considerably increased, and nothing like excessive exudation occurs. If the blood pressure is heightened and at the same time the rate of flow of blood is increased, we do not appear to get much liability to dropsy. If, however, the pressure is increased, and there is some obstruction to the onflow of blood, more especially in the veins, then it is that we appear to have the most potent cause for the development of dropsy or

œdema, which is usually expressed by saying that venous congestion brought about by obstruction to the onflow of the blood, whether in the heart or liver, is the most frequent cause of dropsy. Rate of flow seems to be more of a factor than increased blood pressure.

3. THE CONDITION OF THE BLOOD.—This is undoubtedly an important factor, the thinner the blood and the poorer it is in albuminous contents the more readily does dropsy supervene. As already stated, it may be that the passage of fluid within the vessels is dependent to a certain extent on filtration and to a certain extent on selective process. And if the blood be thinner, then there may be increased filtration. But also a thin blood is a poor blood, and leads to impoverished nutrition of the vessel walls as of the tissues in general, and thus the endothelium of the capillaries is weakened and more readily permits the outflow of fluid.

A further factor to be mentioned in the occasional production of dropsy is the nervous system. There are certain conditions under which localised œdema is brought about by nervous means. Here probably the mechanism at work is not merely altered diameter of the vessels of the part and altered blood flow through the part, but is also some alteration in the condition of the endothelium.

Taking into account then the above-mentioned facts, we can recognise the following forms of œdema, mainly due to altered conditions of the circulation :—

1. *Obstructive*, or as is often termed, *Mechanical* dropsy. This is one of the commonest forms, and is most frequently seen in cases of (*a*) obstructive heart and lung disease ; (*b*) of valvular disease causing obstruction to the onflow of the blood, either by stenosis of the valves or by their incompetence, of which there is regurgitation, and of these various forms of valve disease, mitral stenosis is the most frequent ; (*c*) obstruction to the portal circulation. This is most frequently brought about by fibroid changes in the liver (*cirrhosis*), and also by pressure of tumours upon the portal

vessels at the base of the liver. In the former of these cases the dropsical condition is the more general, affecting all the cavities and leading to anasarca, which especially manifests itself in the lower extremities where the venous obstruction tells most easily. In the latter the dropsy affects only the portal area, namely, the abdomen, and we have ascites without hydrothorax, etc., and without necessarily any presence of anasarca. It will be seen that in all these cases the condition is one of venous stagnation, the blood is propelled into the capillaries and veins and cannot easily pass forwards. As a consequence these vessels are distended, the blood is venous, the walls are probably affected by the modified blood, and from all these causes there is increased outpouring of fluid.

2. INFLAMMATORY ŒDEMA.—In all cases of inflammation, save where the nature of the tissue prevents it, as in bone, the inflammation is associated with increased pouring out of fluid into the part, and very often this increase is so extensive that the lymph vessels cannot carry off the extra amount of fluid which is exuded. I have discussed this subject in my lectures on inflammation, and here would only remind you that such inflammatory exudation has a higher specific gravity and increase in albuminous contents, and has a composition different from that seen in mere mechanical dropsy. The best examples of this inflammatory œdema and exudation are to be seen in cases of inflammation of serous surfaces, and again in inflammation of very loose tissues. A notable example of this form is the œdema glottidis, which may develop in relatively mild cases of inflammation of the glottis. Another notable example is to be seen in the acute rheumatic inflammation of joints and the tissues bordering upon them.

3. HYDRAEMIC AND CACHECTIC DROPSY.—It is possible that these should be separated one from the other, and that one should distinguish more especially the dropsy of Bright's Disease and arterio-sclerosis from that associated with exhaustive illness, for it is possible that in the former the disease of the arterial walls and the altered arterial tension play the most important role. At

the present time, however, it is difficult to make any absolute statement about this matter. According to Dembowsky as opposed to the observations of early observers, mere diminution of the albuminous contents of the blood produces no œdema. Thoma has pointed out that the injection of normal salt solution into the femoral vessels of an individual showing no arterio-sclerosis leads to a much slower development of dropsy in the corpse than where there are arterio-sclerotic changes. Where the latter are present the stream becomes slow, and the legs swell up in a very short time. Thus in cases of sclerosis of the vessels there would appear to be increased friction to the flow of the blood and increased permeability of the vessel wall. In these cases the transudation is characterised by the relatively small amount of albumin it contains and by its low specific gravity. Altogether the abnormal permeability of the vessel walls seems to be the main factor in the œdema of Bright's, arterio-sclerosis and probably also of cachectic conditions.

4. NEUROPATHIC ŒDEMA.—This form is seen at times in cases of trigeminal paralysis, in neuralgia and in hysteria. It is independent of any change in the condition of the blood or of any local disturbance of the tissue, and so can only be ascribed to modified conditions of the vessel wall under nervous influences.

Atrophies and Degenerations.

Besides the hypertrophies and the progressive disturbances of tissue, an important series of changes is to be recognized in the various organs as a consequence of disuse, malnutrition and toxic disturbances. We may have simple atrophy of the cells of an organ, or other evidences of degeneration of those cells, or, thirdly, there may be infiltration by abnormal matters into either the spaces of the tissue or even into the cells of the same. Lastly, there may be what is spoken of as qualitative atrophy, namely, a transfer from a higher to a lower form of tissue; this is seen specially in the various connective tissues. We thus may distinguish between the conditions of atrophy and degeneration and of infiltration and metaplasia.

SIMPLE ATROPHY.

This must be distinguished from the conditions of *hypoplasia* or imperfect development of tissue, and *aplasia* in which there is a congenital lack of development of one or other tissue or organ. It can only occur in connection with fully developed tissues. It may be (1) Physiological. (2) Pathological.

Physiological Atrophy.—This is well seen in the various tissues of the body. One of the first organs to become atrophied is the thymus, later the roots of the milk teeth, and then in adult life we find the ovaries, the permanent teeth, the hair, the bones and muscles all presenting simple atrophy to a greater or less extent at different life periods. Thus the various tissues have a time of maximum growth and a time of decline, and the equilibrium between the various organs of the body is constantly changing; indeed we may go so far as to say that to this different periodicity of the various organs, to the difference in their life periods and to the successive decay and death of individual tissues, we must ascribe the natural or physiological death of the indivi-

dual; we must, that is, recognise that each tissue physiologically has its period of prime followed by more or less atrophy, and, this being so, the time must come when the naturally lessened activity of this or that organ so tells upon the system at large that nutrition reaches a point at which the further adequate action of the still active tissue is rendered impossible.

Pathological Atrophy Causes.—(*a*). Passive.—From pressure, *e. g.*, the atrophy of the foot in Chinese women; in the tissues surrounding aneurisms and enlarged Pacchionan bodies.

(*b*). Malnutrition.—From poverty and hunger; digestive disturbances, more especially stenosis of œsophagus or pylorus; exhausting evacuations, etc.

3. Lessened function and disuse, *e. g.*, atrophy of lower jaw after loss of teeth; atrophy of muscles of limb following upon immobilization of limb after fracture, etc.

4. Active atrophy.—(1) Following upon excessive use of a part, *e. g.*, muscles and various glands. (2) Caused by poisons or infectious diseases. (3) Nervous trophoneurosis, *e. g.*, the atrophy following upon spinal paralysis; notably the bed sores accompanying spinal disease. (Such bed sores are not merely due to atrophy from pressure. The atrophy in spinal disease and the development of bed sores is very much more rapid than is the case in mere exhausting diseases.)

The changes in these different forms of simple atrophy brought about by the causes above enumerated vary somewhat in the different tissues. We obtain both a qualitative and a quantitative change in each organ, a diminution in the number of the specific cells of the organ, and in very many cases shrinkage and other changes in the individual cells. Seen under the microscope, the protoplasm of the cells may show no physiological change, though very frequently there is pigmentation. This pigmentary "infiltration" is due to the fact that the pigment of the cells does not disappear to the same extent as do the other elements, hence pigmentary atrophy and simple atrophy are very closely connected. In simple atrophy

of muscle it is the body of the fibres which disappears to a very considerable extent, and the interstitial tissues, not being affected to anything like the same extent, appear to be increased ; the increase, however, is only relative. In the liver the cells become very small and show marked pigmentation, which again, as above mentioned, is largely relative ; in the heart muscle this pigmentation is also very marked ; in the kidney the tubules become smaller, until only minute double rows of nuclei remain, and finally these may disappear or the tubules collapse. In fatty tissue, the process is rather remarkable ; the fat as it becomes absorbed separates into smaller drops, and the nuclei of the cell multiply, so that in place of one cell filled with fat there may be present several cells resembling large hyaline leucocytes. In some cases this process is accompanied by an œdematous condition of the tissue, so that it has a more or less gelatinous appearance, the so-called serous atrophy of fat, not unfrequently seen in the epicardial fat of the heart and in the white marrow of bones in old people and in advanced cases of osteomalacia.

In nerve cells, atrophy first shows itself by shortening and disappearance of the numerous finer dendritic processes. The cell becomes shrunken and pigmented, and finally the main processes become diminished, and their lateral buds disappear. In the medullated fibres, there are accompanying changes of the sheath of Schwann. The medulla breaks up into myelin droplets, the nuclei of the sheath multiply, the axis cylinder breaks up into fine fibrils, and eventually all that is left is a line of cells developed from the neurilemma.

In bone there is absorption of the bony tissue in part through the action of osteoclastic cells eroding the bony plates, and in part (in senile conditions) by a process of decalcification of the layers of bony tissue nearest to the medullary spaces. This osteoid substance undergoes resorption. In both these ways the medullary cavities become enlarged, and the bone rarefied. At the same time the fat cells of the medulla undergo a gelatinous or serous atrophy.

CLOUDY OR ALBUMINOID DEGENERATION.

This is mainly confined to the specific cell structures of muscle and glandular organs. On removal of the organs from the body they are noticed to have a rather fuller appearance, and on sections they have lost their lustre; thus muscle especially appears as though it had been dipped for a moment in boiling water. Under the microscope the cells have a cloudy appearance, and in consequence are indistinct, the individual cells are swollen, the cloudy appearance resolves itself into a mass of very fine granules—a molecular deposit within the cell substance. The nature of this is to be determined by micro-chemical means. The cloudiness is not affected by alcohol, ether, clearing fluids or other substance which dissolves fats; on the other hand, treatment with 1% of acetic acid or caustic potash causes the cell to become cleared. Evidently, the deposit is of an albuminous nature, and this treatment converts the fine granules into acid or alkaline albumin, which is soluble. As Thoma points out, the same condition sometimes affects the cells of interstitial tissue of bone and cartilage; there is the same cloudiness seen with indistinctness of the nuclei. In the most extensive stages the nuclei may be so modified that they no longer stain. This condition is found in various febrile and zymotic diseases. The high temperature alone does not cause it, but the condition seems to be associated with increased or altered metabolism in the cells. Thus we find it also in diphtheria, where there may be very little high fever. After burns, where apparently some toxic substances enter the blood from the burned tissues, it is also recognizable. It may be found again in the first stage of poisoning by certain chemical substances, such as phosphorus. In short it appears to be due to sundry toxic agencies. This condition may easily pass on to and accompany another and more advanced form of degeneration, namely, fatty degeneration.

THE HYDROPIC OR DROPSICAL DEGENERATION.

Such a degeneration is to be seen in the cells of the kidney tubules after poisoning with cantharidin, also in some cases of scarlatinal inflammation of the kidneys, but it is perhaps best marked

in not a few forms of inflammation of the skin, notably in vaccinia and small-pox. In these conditions the cells of the deeper layer of the skin become in the first place swollen and cloudy, next they become vacuolated, the vacuoles being filled with clear fluid, and next the nuclei lose their power of staining, the vacuoles run together, and the cells are represented by the thin membrane surrounding a cyst or vacuole filling the whole of the cell.

FATTY DEGENERATION.

Cloudy degeneration as above stated frequently a precursor of fatty degeneration.

Such fatty degeneration or metamorphosis of the cell protoplasm may be either a physiological or pathological process. Examples of *physiological* fatty degeneration :—

In the mammary gland during lactation, the cells become filled with fatty globules and then, breaking down, those globules form the fatty globules in the milk. It may be urged that this really is not a metamorphosis of the protoplasm, but that fat is brought to the cells by the blood. This is in part true, but in part also the formation of fat here seems to be associated with the breaking down of the cell protoplasm notably in the first milk or *colostrum*. The same is true in the production of sebum, the cells of the sebaceous glands undergoing very similar changes. Other examples are to be seen in the muscle fibres of the uterus during involution after pregnancy and in the cells of the ruptured Graafian follicle in the formation of the corpus luteum.

Pathologically we find fatty degeneration occurring in conditions where there is great lowering of nutrition. It occurs in the severer forms of anæmia, in pernicious anæmia and purpura hæmorrhagica ; in these conditions, especially, the heart muscle is affected. In certain zymotic diseases it is well seen, notably in diphtheria and typhoid. It may occur as a result of certain poisons, notably phosphorus and arsenic. In these later cases not only the heart but the glands of the body, especially the liver and

the kidney, show well marked degenerative change. It is interesting to note that fatty degeneration of the heart muscle occurs when there is no such degeneration to be met with in other organs. Such fatty degeneration as already stated may be due to either general malnutrition of the body or to local malnutrition, as for example in cases where in old people there is atheromatous narrowing of the arteries. We thus get fatty degeneration of the heart from this latter cause frequent in old people. Here clearly what has happened has been that the individual fibres, not receiving adequate nourishment, and being called upon to do constant work, undergo an actual breaking down of their own protoplasm, and the fat seen in the fibres is the result of this metabolism of the cell substance. Where there is general malnutrition of the body as in anæmia and leucæmia, it is somewhat more difficult to explain why the heart especially becomes affected. Probably in these cases, the blood being impoverished, the heart has to perform increased work and the blood has to circulate more rapidly in order to meet the needs of the organism, and this increased work with impoverished nutrition leads to a relatively greater malnutrition of this than of any other organ. We have increased disintegration of the muscle substance, combined with simultaneous diminution of the oxydation of the same, and as a consequence albuminoid substance, fat, leucin, sarcolactic acid, etc., are formed. In short, fatty degeneration is everywhere the result of imperfect nutrition of the cell with imperfect compensation of the waste brought about by the working of the cell. Secondly, there must be an insufficiency of the oxygen supply of the blood or incapacity on the part of the cell to take up sufficient oxygen to oxydise the fat formed by the breaking down of the cell proteids, and so fat accumulates as a deposit within the cell. In connection with febrile diseases and with the toxins of infective micro-organisms, as also in the action of phosphorus and arsenic, we can see some of the stages of this breaking down, *i.e.*, we recognize the primary stage in which there is a deposit of proteid matter in the cell (cloudy degeneration), and later this gives place to a fatty change.

Appearance of Tissue undergoing Fatty Degeneration.

The appearances vary somewhat in the different tissues: in muscle, notably in the heart muscle, we find minute scarcely recognisable droplets of fat scattered through the cell, often appearing to be in lines corresponding to the longitudinal striæ. These droplets are throughout very small; in the liver and the kidney they may be of very variable size, in general they are small, though sometimes, as for example in phosphorus poisoning, they may attain a considerable size. I shall have more to say upon this point in speaking of fatty infiltration.

As pointed out by Mott, another form of fatty degeneration is to be found in degenerated nerve fibres. Six to twelve days after section of the nerve fibre, the myelin or medulla, which before would not stain with osmic acid, now stains well, and he is of the opinion that here the fat has been produced by a splitting up of the lecithin, which is not a proteid, but more allied to the alcohols, which is an important constituent of nervous matter.

Detection of Fat.

There are two useful methods for detecting fat, even when present in minute quantities in the tissues. Sections of these tissues either prepared or kept in some fluid other than alcohol (for alcohol slowly dissolves the fat) may be treated (1) with 1% of osmic acid, or (2), the sections may be treated either with a weak solution of caustic potash or of acetic acid. Either of these will dissolve and clear up all the proteid matters of the cells, and the fatty globules will stand out as brought highly refractile particles.

It is often difficult to say whether, when we meet with fat in a gland cell, we are dealing with a fatty metamorphosis or degeneration of the protoplasm of that cell, or whether we are dealing with a storing up of fat that has been brought to and been absorbed by the cell. Where there is a storing up, there in general fat globules are larger than where there is a breaking down. In the

liver it is frequently more difficult to make the determination, though this may be laid down for the liver and other organs, that, where there is a storing up, the organ is rather larger than normal; a breaking down indicates degenerative processes in the tissue, and the organ is smaller, somewhat atrophied and flabby. In the liver especially we meet with this difficulty, that after all, where we have storing up of fat and infiltration, it is most probable that the cells do not receive the fat exactly as it is deposited, but have the power of forming it from some precursors of a different nature. We see evidences of this in the fact that the dog and other animals has a fat which is composed of different proportions of palmitic, stearic and oleic acids. If we feed the animal upon any one of these fatty acids, it will lay down in its tissues the fat composed of the normal proportions of all three, that is to say, that having absorbed the one fat, through cell activity it has taken this up and broken it down into the other, hence probably fatty "infiltration" is not merely a process of simple absorption of fat from the food, but is an active process of cell metabolism, the proteid matter of the cell breaking down into a nitrogen containing part, urea for example, and into a non-nitrogenous portion (fat), and as we can have thus a normal and physiological fatty degeneration of some cells and a pathological infiltration of others, and as in both the process seems largely to be due to cell activity, the distinction between these two conditions (in glandular cells at least) would seem to be, if not far fetched, at least not the simple matter usually described in the text books.

Fatty Infiltration.

There is, however, a form of fatty infiltration about which there can be no doubt, a form in which the fat does not accumulate in the specific cells of the tissue, but between them. There is an increase in the number of true fat cells of connective tissue origin in various parts of the body. We see this more especially in connection with the muscles both skeletal, in cases of pseudo-hypertrophic muscular paralysis, and cardiac, in cases of general lipomatosis or obesity, or often where there is not such very extensive deposit of fat in other parts of the body.

In these cases we get the interstitial connective tissue cells undergoing a transformation and becoming filled with fat, so that the large and very characteristic fat cells are found to have *infiltrated* between the specific cells of the tissue. This is the true fatty infiltration, but you must remember that, as the liver cells under very similar conditions also become very full of fat, we also speak of a fatty infiltration of these, though here the fat is *within the cells.* In such cases the main process would seem to be an increased absorption of excess of non-nitrogenous food material, so that it cannot all be used up by the tissues, and becomes stored as fat in various regions within certain connective tissue cells, and also in the cells of the liver. Here then in such cases of fatty infiltration we have primarily to do with the storing up of more food material than can immediately be utilised. We are in no sense dealing with a degenerative process, although the very presence of this excessive number of fat cells may impede the proper working of the specific cells of the tissue, and so lead secondarily to impaired action of the same and to diseased conditions. Such fatty infiltration may again occur where there is already present a certain amount of disturbance; we get it notably in the liver in cases of alcoholism and of tuberculosis. In the former of these cases what happens apparently is that the alcohol taken by the alcoholic is largely utilised as a food stuff, while at the same time it lowers general metabolism of the body. From both causes the ordinary food stuffs which have been absorbed are not utilised, and these are laid down in the tissues as fat. In tuberculosis, on the other hand, what we have to deal with primarily is lowered metabolism. The food stuffs are insufficiently oxydised, and thus the fat formed in the liver cells is not burnt up, and gradually accumulates.

Glycogenous Infiltration or Degeneration.

Under normal conditions glycogen is to be found in the liver cells and also in the muscle fibres, and in minute amounts in other tissues of the body; in fact, glycogen is one of the forms of meta-

bolism of carbohydrates in the tissues, and is both manufactured from soluble carb hydrates brought as food to the cells, and is, as occasion requires, converted again into sugar. It is questionable whether, under any conditions, the presence of glycogen in the cell should be regarded as a degeneration, or whether more truly it is not of the nature of a deposit. It is found in the tissues as a hyaline substance, generally in the form of globules of different sizes, which are soluble in water, so that care has to be taken in the preparation of tissues in order to preserve it. The characteristic reaction is by treatment with an alcoholic dilution of tincture of iodine, when the globules of glycogen assume a brownish red colour.

Pathologically it is especially in diabetes that abnormal deposits of glycogen are found in the tissues. The one region where such are especially seen is the kidney, and here more especially in the cells lining the loops of Henle. The cells here may be so crowded with glycogen that, when it is dissolved out, a simple frame work or coarse network of protoplasmic filaments is left. In diabetes also it is pointed out that the brain tissues contain increased glycogen, while, on the other hand, the liver and heart which normally contain this substance are almost completely deprived of it. In inflammation the leucocytes contain the substance. I will speak further concerning this in connection with the subject of amyloid degeneration. In other conditions in which there is considerable drain from the tissues, there is both glycogen in the leucocytes and also dissolved in the blood. In certain tumours, more especially in tumours of the suprarenal, there is present a considerable amount of glycogen in the tumour cells.

Mucoid Degeneration.

Mucins are nitrogenous compounds, which upon decomposition break up into albuminoid substance and carbo-hydrate moiety or residue; they are soluble in alkaline carbonates and dilute caustic and in lime water, while they are precipitated from weak alkaline solutions by acetic acid and alcohol, forming stringy masses with the latter reagent.

Microscopically this mucin is homogeneous and transparent, is not affected by carmine, but is tinged by the basic aniline dyes.

Physiologically we find that these mucins are normal products of the metabolism of the various cells; we may have them present under two conditions:—

1. In the interstices of tissue.

2. Within the active gland cells of a glandular tissue. Here in these cells they would appear to be present, not as fully formed mucins, but in spherules of an antecedent body, which is spoken of as *mucinogen*, and which only upon excretion assumes the features of mucin proper; from these cells under normal conditions the mucin is excreted. Whether in these two cases of interstitial and glandular development we are dealing with one substance is doubtful; it is very probable that there are several mucins more or less closely related chemically.

Examples of the first class of physiological formation is to be seen in developing tissues. Here growing connective tissue cells are often widely separated by a mucinious stroma. This is especially well seen in the Wharton's Jelly of the umbilical cord. As the tissue gains maturity, this mucin is replaced by connective tissue fibrils.

Examples of the second class are more frequent; all columnar-celled epithelium would seem capable of storing up mucinogen, and we can thus recognize the turgid "goblet cells" all along the alimentary tract from the stomach downwards.

Pathologically we find examples of the first class more especially in inflammatory new formations. Granulation tissue is practically a developing connective tissue, and here with the development of fibro-blasts one has the mucin-containing stroma which later gives place to a fibrous stroma. In the early stages of myxœdema we find also an increased amount of interstitial mucin, and again in certain connective tumours notably in lipomata (myxolipomata), chrondromata (myxochrondromata) and fibromata (as of the uterus.) In tumours of the posterior nares and pharynx, the growth may be wholly composed of mucoid tissue (pure myxomata).

Pathological examples of the second class are also to be met with in inflammation. Here in the early stages of inflammation of a columnar-celled epithelium, we find that there is a great increase in the amount of mucin formed and excreted by the epithelial cells so that the free surface may be covered by a thick layer of mucus. In certain forms of tumours also we find this excessive production and excretion of mucin, notably in multiple ovarian cysts which are bounded by columnar epithelium and are filled with mucinous fluid, the result of the excretion of these cells. In certain forms of cancer also, notably in cancers originating from a columnar epithelium, cancers of the rectum and of the intestines in general, we are liable to have the new formed cells swollen up with mucin, and undergoing thus a mucinous degeneration.

HYALINE DEGENERATION.

We now pass on to a class of degenerations which it is very difficult to classify, inasmuch as a large number of apparently different chemical changes and modifications of protoplasm are included under the one term, while concerning the chemistry of these bodies we have very little information, and the different authorities differ very considerably in their treatment of the subject. Thus we have included into this term what some authorities distinguish as colloid degeneration, also an extra-cellular degeneration seen more especially in connection with the smaller arteries, and thirdly (not to mention some still further and less frequent varieties,) a homogeneous and hyaline transformation of the fibrin of coagulated blood. It will be well perhaps to treat these in order.

A.—COLLOID DEGENERATION is evidently closely allied to the mucinous, and probably is due to a later change occurring in the product of intra-cellular mucin-like production. Such colloid material occurs physiologically within the vesicles of the thyroid gland. This material is distinguishable from mucus in that it does not swell up in water, and it is not coagulated by acetic acid, and that alcohol and chromic acid render it opaque.

Pathologically we find the same substance present in abnormal amount in the greatly dilated vesicles of the thyroid in some cases of enlargement of this organ. We find a substance having very similar characters filling up the tubules of the kidney in some cases of chronic nephritis (colloid casts), and a somewhat similar substance is found in the spaces of certain forms of cancer, more especially in cancer of the stomach and intestines, in which we find the cells completely degenerated and replaced by this colloid material. In these cases there is frequently a certain amount of swelling when portions are placed in water, and evidently we can have transformation from a mucoid degeneration of the cancer up to the typical colloid cancer.

B. Interstitial Hyaline Degeneration.

We have here most frequently to deal with a degeneration of the cells of the smaller vessels in which there is a deposit of a homogeneous firm and transparent material external to the endothelium of the vessels. Occasionally the deposit occurs in little drop-like masses just outside the vessels. The appearances generally are very similar to those seen in amyloid degeneration, but, as will be pointed out later, the material thus laid down does not have a typical amyloid reaction. Occasionally also we meet with a similar degeneration in fibrous connective tissue, causing an increase of the volume of the same and the production of relatively large areas, which are firm, homogeneous and hyaline, all the cells of the part and the fibres becoming completely unrecognizable. With Van Gieson's method, such hyaline material takes on a brilliant red colour.

Evidently what we have to deal with in this series of cases is one form of local death of the tissue, and the hyaline change is therefore not so much a degeneration as one of the results of necrobiosis or gradual death of the tissue. It is not the degeneration, but the result of the degeneration. It should be added that perhaps one of the most frequent and most easily recognized

orms of such hyaline degeneration is to be seen in the glomeruli of the kidney where there has been interstitial nephritis with fibroid change, and the blood supply of the glomerulus has been cut off by the contraction of the fibrous tissue.

[See Mallory and Wright, p. 358, for a good *resumé* of staining reactions of different forms of Hyaline Material.]

C. Hyaline Degeneration due to Change in Coagulated Blood.

As pointed out by Von Recklinghausen in thrombosis, we frequently meet with a form of hyaline degeneration. It is one of the secondary changes in thrombosis; at times it may occur in diphtheria, the fibrin in diphtheritic inflammation of a surface being deposited not in the form of fibrils, but in clear droplets of hyaline material, which running together form relatively large areas of this material. In white thrombi, especially where we have to deal with a process due to blood platelets, this hyaline change is especially manifest. A somewhat similar form of hyaline degeneration is to be seen in the kidney in the formation of hyaline casts. These casts are homogeneous, and are at times very abundant. It used to be thought that they were the result of a fibrinous exudation, but it is often possible to recognize what appears to be the first stages in their development. At times we are able to see that from the central margin of the epithelial cells of the convoluted tubules there are given off fairly large and singularly transparent globules, and we may occasionally find a tubule filled with these extremely delicate globules, and in the same kidney can see other tubules filled with transparent hyaline material. Apparently then the casts are formed by effusions of these droplets or spherules. What is the exact nature of the process we do not know, but it is clearly one form of degeneration of the renal epithelium.

D. Vitreous Degeneration.

In muscle also a somewhat similar hyaline degeneration can be recognized. As J. Arnold pointed out, after rupture of healthy muscle fibres, the torn portions become swollen, hyaline and homogeneous. A somewhat similar, if not identical degeneration, is to be seen in cases of zymotic diseases, more especially in typhoid. The individual fibres swell and become peculiarly transparent and wax-like with a loss of evidence of striation. This is known as Zenker's Degeneration. It is questionable whether this degeneration is secondary to rupture of the fibres, or whether, when the fibres have undergone this degeneration, they are peculiarly liable to rupture. It may here be pointed out that such rupture of the fibres of the rectus abdominis muscle with subsequent hæmorrhage is not at all unfrequent in cases of typhoid.

AMYLOID DEGENERATION,
or more correctly, Amyloid Infiltration.

There are certain well ascertained facts with regard to this amyloid change which may here be given, but as with the other degenerations we are still far from knowing why exactly certain conditions should lead almost inevitably to the development of this very remarkable condition.

Features of the Degeneration.

The conditions under which it is found.—Amyloid degeneration may be either local or general; the latter is the form which we most frequently meet with.

Generalised Amyloid Change.

Causes.—This condition is most frequently met with in diseases which are characterised by long-continued draining of albuminous matter from the system. Thus, first and foremost, it is found in cases of chronic ulcerative tuberculosis and of the different forms of tuberculosis, Pott's Disease, or cold tuberculous

abscess is the condition most surely leading to its development. It has also been found in cases of syphilis, of long-continued lactation, and in some few cases of chronic Bright's Disease and of leuchæmia. The organs especially affected are the spleen, and next, most frequently, the liver and the kidneys. It is also found in the heart, the intestinal walls, suprarenals and other organs.

REGIONS OF DEPOSIT.—In all these cases the vessel walls, and especially the walls of the middle coats of the small arteries and the walls of the capillaries, are especially affected. It is in this region that there is a deposit of an hyaline, transparent material, which may be present in relatively very large amounts. The deposit is extracellular; in the finest capillaries it occurs on the outer side of the epithelium. More rarely in extreme cases of amyloid degeneration, the basement membranes of glandular organs (in the kidneys of the tubules) may be affected; and more rarely again it would seem evident (in the liver for example) that the actual specific cells ofthe tissue may thus become the seat o fthe change; about this there issome doubt. The process may continue to such an extent that the cells of a tissue may be so pressed upon by the deposit, and also be so badly nourished that they undergo complete atrophy, so that large areas may be seen in which there is almost entire loss of cell substance and a complete replacement by these long irregularly cylindrical masses of amyloid. When a capillary is affected the deposit is often not evenly disposed round the capillary, but occurs in greater amount on one side than on the other.

REACTIONS.—The amyloid material takes on characteristic eactions. If a moderately dilute solution of tincture of iodine dilute the tincture of iodine with water untilit is of the colour of brown sherry) be poured over the surface of the organ affected with this disease, then by reflected light the regions which are the seat of amyloid degeneration take on a strong mahogany brown colour. Sometimes, but not always, the subsequent employment of sulphuric acid leads to the production of a blue colour, and from this reaction it was that Virchow spoke of this as amyloid degen-

eration (from AMYLUM starch). Where sections are made, then, by transmitted light, the unaffected tissue appears of a dark brown, and the amyloid material is hyaline and pale yellow in colour. Sections treated with certain of the basic aniline dyes take up the stain characteristically. With gentian violet for example, the amyloid material takes up a more purple reddish colour; the unaffected part has a paler stain, and if tannic acid or other weak acid be employed to fix the stain, then the amyloid material has a rose colour, the unaffected tissue a somewhat greenish tinge.

GROSS APPEARANCE OF ORGANS AFFECTED WITH THIS DISEASE.

Where the disease is at all extensive, the organ (liver, spleen or kidney) is larger than normal, the edges are rounded, the colour is pale and the organ is firm (this is not always the case with the kidney, which sometimes may be rather soft from associated advanced degeneration of the epithelium, but is the rule with the liver and the spleen). It cuts firmly, and on section it has a bacony or lardy appearance, hence the term *lardaceous* degeneration.

CHARACTERS OF THE INDIVIDUAL ORGANS.—The spleen may show three types of disease:—(*a*) The Malpighian bodies may be especially affected, stand up on section like small grains of boiled sago, hence the term, "*Sago Spleen.*" (*b*) The walls of the splenic sinuses may be the primary seat of the deposit, and here, the affection being more generally distributed, the appearance is rather that of boiled bacon, hence the term, "*Bacony Spleen.*" (*c*). Both sinus walls and Malpighian bodies may be affected.

THE LIVER:—The condition shows itself first in the intermediate zone of the lobules, where the small branches of the hepatic artery join with the capillaries from the interlobular branches of the portal vein. Here it is along the walls of the small vessels that the deposit takes place. In more severe cases the affection may extend along the vessel walls of the whole of the lobule.

THE KIDNEY.—It would appear that most frequently the first portion to be affected is the middle coat of thesmaller arterial branches, notably, those in the cortex, and among them especially

the afferent vessels of the glomeruli. Next most frequently the large capillary loops of the glomeruli are the seat of the change, until sometimes the whole glomerulus appears as little more than a mass of amyloid material. In rarer cases the straight vessels of the medulla and the basement membranes of the collecting tubules are affected. In the heart, intestines and other organs, it is along the arterioles that the change is most marked.

NATURE OF THE AMYLOID MATERIAL.—This is singularly resistant to various chemical substances, and thus Kühne and Rudneff, by digesting off all other proteid material (in the liver for example) by the gastric juice, have gained it in a relatively pure state, and by decomposing it have come to the conclusion that it is not a pure proteid, but, like the mucins, and probably also the hyaline substances, it would seem to consist of a combination of the proteid with some carbo-hydrate substance. We meet with somewhat similar substances as a result of degenerative processes in plants—the various gums—and these allied animal substances have been spoken of as "animal gums." It has further been found that if amyloid material be inserted into the body cavities of animals, it gradually becomes changed and takes on the characteristic staining properties of hyaline material. So also cases are on record in which some portions of the tissue, kidney for example, have shown hyaline reaction, and others amyloid. There would thus seem to be a close relationship between the amyloid and hyaline substances. Now glycogen is a carbohydrate substance, and Czerny has pointed out there appears to be some relationship between the glycogenous "degeneration" and the development of amyloid. As I have already stated, pus cells contain glycogen, or a precursor of the same, and in suppurative disease and in various atrophic disturbances and cachexias, the circulating blood contains glycogen. Experimentally, by lowering the temperature of animals, by inducing severe anæmia, or again by subcutaneous injections of turpentine, he could increase the glycogen in the blood. It was in the last set of cases that he found also by chance that he induced a development of amyloid degeneration.

Both glycogen and amyloid material react with iodine, and are turned brown, and in the kidney of the hibernating frog Lubarsch noted an intermediate body. Certain interstitial cells contain granules staining with iodine, and like glycogen dissolve by the saliva, and at the same time give the gentian violet test for amyloid. Thus it is assumed that those conditions which lead to the increased production or appearance of glycogen in the blood, and especially in the circulating leucocytes, lead eventually to the development of amyloid changes in the tissues, and it is suggested that glycogen is essential for the production of this amyloid material, which, as I have already stated, would seem to be a compound of proteid material and carbohydrate substance. These observations of Czerny, Krawkow and others, are recent, and require further confirmation. Kanthack and others have failed to obtain the same results, but it must be urged that one positive is worth very many negative observations.

It should be added that more that one observer has found that occasionally the inoculation of animals with relatively large and repeated doses of bacterial growths leads to the development of this form of degeneration. The pyococcus aureus, the B. pyocyaneus, the anthrax bacillus, etc., have all been inoculated, and have been found to lead occasionally to either local or generalised development of deposits of the amyloid substance. The process in all these cases has been the development of chronic suppurative disturbances.

Local Amyloid Degeneration.

Occasionally deposits resembling amyloid material in their staining and properties are found strictly localised. Such deposits have been found in syphilitic gummata ; they are comparatively common in the form of rounded globules of the prostate gland ; they have been found also occasionally as little rounded concentric bodies in the lungs, more especially in cases of chronic congestion. Somewhat similar little globules are not infrequent in the brain and spinal cord of elderly people.

Pigmentary Infiltration and Pigmentation.

Under this heading we have to deal with a series of conditions in which there is deposit within the tissue of granules of pigments of various natures. Under normal conditions we find that pigment or colouring material is present in certain of the tissues of the body. Some of this pigment or colouring material it is scarce necessary to mention here is in solution (the hæmoglobin of the blood and the pigment of the bile when it is excreted by the liver cells) but some even in normal conditions is present in a precipitated form, notably the melanin of the choroid of the eye and of the deeper layers of the true skin. A similar pigment is also to be found in the choroid plexus of the brain, and in some of the lower animals collections of cells containing pigment are to be found in other internal organs.

Pathologically we may distinguish between several different forms of pigment abnormally deposited. Thus we have (*a*) colouring matters deposited in the tissues derived from the hæmoglobin of the blood, (*b*) colouring matters (in general soluble) derived from the bile and thus indirectly from the blood, (*c*) abnormal presence of melanin, and (*d*) extraneous pigmented material taken into the organism from the exterior and deposited in one or other tissue.

Pigment derived directly from the Blood.

When there is any hæmorrhage within the cavities of the body, the red corpuscles thus removed from the circulation undergo a series of necrotic changes, and almost the first change which occurs is that the hæmoglobin contained by these red corpuscles becomes dissolved out in the surrounding fluid. The first stage therefore is that there is liability for surrounding tissue to be tinged with this liberated hæmoglobin. We do not see much evidence of this first stage ; though occasionally in the early stage of a skin wound this

inbibition of the hæmoglobin gives to the superficial tissue a peculiar reddish or purplish tinge. Very soon this hæmoglobin (if it does not pass away in the lymph) as a result of certain chemical changes becomes precipitated in the form of yellowish-brown brightly coloured rounded granules insoluble in water which are known as *Hæmosiderin.*

HÆMOSIDERIN is a name given to the brownish, brightly coloured granules appearing thus in connection with hæmorrhages. These are insoluble in water and contain iron. This iron can be detected by the action of hydrochloric acid and potassium ferrocyanide when they become blue, owing to the formation of "Prussian Blue." It is evident that they are a form of albuminate of iron. Similar albuminate of iron is to be found normally in organs which are associated with the breaking down of blood corpuscles, notably in the spleen and liver cells.

In large quantities, however, these granules are found in connection with extravasations. If the extravasations are small we find the hæmosiderin granules only. In larger collections of blood a crystaline product, *Hæmatoidin*, is produced. According to Thoma this latter is formed where oxygen is small in amount, the former where there is relatively more oxygen. Hæmatoidin is present in the form of minute rhombic crystals of a deep reddish colour, and differs markedly from the hæmosiderin in the fact that it contains no iron. It is in fact identical with bilirubin. That the liver cells contain within them granules identical with hæmosiderin, and at the same time excrete bilirubin, would seem to be ample evidence that something beyond mere relative amount of oxygen present is associated with the development of these two forms of pigmentation. I shall have more to say with regard to hæmatoidin or bilirubin in discussing the subject of icterus; here I would simply point out that the substance identical with bilirubin can be produced outside the liver by the destruction of blood corpuscles.

Chloroma and other rarer Pigmentative derived from the Blood.

In many tumours of different natures upon section a greenish colour is developed, and this green colour has caused these tumours to be spoken of as being chloromatous. The term is vaguely employed to denote both the tumours and the peculiar characteristic of the tumours. This green coloration which is usually diffuse would again seem to be a modification of the blood pigment, and indeed in large tumours where there have been hæmorrhages frequently outside the hæmorrhagic area the sections assume this greenish tinge.

Another condition is a pigmentation of the cartilages of the body, which has very rarely been observed, and which has received the name of *Ochronosis*. Here all the cartilages have been found black, pigmentation being due to the granular black or brownish pigment partly in solution and partly granular. This pigmentation seems to be due to the absorption of disintegrated blood pigment from the circulating blood.

Yet another condition is that called by von Recklinghausen "*Hæmochromatosis*." This condition is moderately rare, and has been found in connection with cancerous and cachectic conditions and cirrhosis of the liver. Here what is observed in the presence of the iron-containing pigment, more especially is the non-striated muscular tissues of the body, especially of the small intestines, and again in the heart; in more extreme conditions it is found in the liver, the pancreas, lymphatic and salivary glands, and in the most extreme conditions is associated with a somewhat bluish or slaty pigmentation of the skin. As above said, this is an iron containing pigment, and according to the recent work of Lubarsch it would appear to be due either to absorption of pigment from large hæmorrhages or again from multiple small hæmorrhages, more especially along the intestinal tract.

Icterus or Jaundice.

By Icterus we understand the yellowish discoloration due to the diffusion of the pigments of the bile from the blood into the

various tissues, and accompanied by an excretion of the bile pigments in the urine with or without bile salts. With this especial feature of the discoloration of the tissues by the pigment there are associated various general symptoms referable to:

1. Disturbances of the liver and gastric functions.

2. Absorption of the bile from the bile passages as a result of impeded outflow.

The pigment of the bile is *bilirubin*, which is now generally admitted to be identical with hæmatoidin. It contains no iron, and in its pure form is insoluble in water, alcohol and ether. With this pigment are associated other closely allied forms, which apparently differ only in the amount of oxygen in their composition, namely, biliverdin, bilifuscin, etc. This pigment is formed physiologically in the liver, and, there can be no doubt, from the hæmoglobin of broken-down red corpuscles. Normally this pigment cannot be detected either of the portal vein or of the hepatic arteries save, according to Gamgee, in the horse's blood serum. Normally also the pigment passes from the liver cells into the bile ducts and so into the intestine, where it is partly transformed into urobilin, and much of it is voided. Some urobilin, however, is apparently resorbed, and, as Jaffe has pointed out, it is invariably present in the urine. Under abnormal conditions, as above stated, we may have this pigment and even the bile salts passing into the blood. As was pointed out so long ago as 1809 by Saunders, this passage of the bile into the blood is not direct, but occurs through the lymphatic system. If the bile ducts be obstructed experimentally, jaundice will supervene in a few hours. If, as Vaughan Harley has shown within the last few years, the thoracic duct be ligatured at the same time, it may be days before such jaundice shows itself in the dog. Thus in the production of jaundice the course of events is for there to be some obstruction to the outflow of the bile pigment elaborated by the liver cells; the excess of this now pours into the lymphatics of the liver and by them is conveyed into the larger lympathic ducts, and so through the thoracic duct into the blood.

THE TISSUES AFFECTED BY JAUNDICE.—The first tissue which becomes noticeably affected is the white conjunctiva, next the skin, which may be stained anything from a bright yellow through green to almost brownish black. The various glands, salivary, mammary, renal, etc., take up the pigment and excrete it; the bones are but very slightly affected, as also characteristically the brain substance.

FORMS OF JAUNDICE.—It has usually been taught until recently that jaundice might be due to one of two causes, either to (1) the obstruction to the outflow of bile from the liver, or (2) the increased production of the precursors of the bile pigment by destruction of the red corpuscles. Thus it has been customary to classify icterus as either *hepatogenous* or *hæmatogenous*. But, as already stated, the bile pigments proper are only formed in the liver, hence, if increased destruction of red corpuscles leads to jaundice, it only does so by the intervention of the liver cells, and thus it is more correct to divide icterus into (1) *hepatogenous*, (2) *hæmo-hepatogenous*. Hunter, who is the latest and most capable authority on the subject, even doubts whether we can truly speak of the hæmo-hepatogenous jaundice, or, to state it more correctly, he is inclined to believe that all cases of jaundice are brought about by some obstruction. In the simpler obstructive forms this is primarily in the larger bile ducts. In the so-called hæmo-hepatogenous forms, it takes place by the excretion of a thick glairy catarrhal product in the finest bile capillaries, whereby they become temporarily blocked. While inclined to accept this view that jaundice proper only occurs where there is some disturbance of the excretion of bile, it must be admitted that it is possible that bilirubin can be formed by the breaking down of the blood corpuscles, in hemorrhage for example, and that even if bile pigment proper does not circulate in the blood, we have conditions in which there is an increased destruction of red corpuscles and a liberation into the blood-destroying organs like the spleen of pigment substances, which are to some extent the precursors of the bile pigment proper. It is thus quite possible that we must recognize also

certain *icteroid* conditions, in which pigmentation of the tissues is due, not to bile pigment proper, and is not associated with liver disease, but is due to the circulation of increased amounts of soluble pigment in the blood. Very probably a slight tinging of the skin, which we recognize in cancer and extremely exhaustive diseases, in advanced septic cases, and again in pernicious anæmia, is due to the presence of such modified blood pigment, and not to hepatic disturbances. There is a certain amount of evidence pointing to the fact that in these cases the pigment material is of the nature of urobilin. Ault has pointed out that the jaundice following the action of certain poisons (phenylhydrazin and metaphenylendiamin) is due to pigment formed in the spleen and carried through the liver into the general circulation.

That under ordinary conditions the action of the liver is necessary to the production of true jaundice is shown by the observation of Minkowski and Naunyn on geese, that if the liver be removed, as it can be in these animals without completely destroying the portal circulation, then conditions which ought to favor the production of hæmo-hepatogenous jaundice are not followed by jaundice.

We now pass on to discuss some of the main forms:

1. Hepatogenous or Obstructive Jaundice.

Such obstructive jaundice may be produced in several ways by obstruction of the main bile ducts:

(*a*) By gall stones and foreign bodies.

(*b*) By cholangitis or inflammation of the main bile ducts. Such inflammation may be catarrhal (acute or chronic) or suppurative.

(*c*) By tumours of the gall bladder and ducts.

(*d*) By tumours of the liver pressing on the main ducts.

(*e*) By tumours of the pancreas obliterating the duodenal orifice.

(*f*) By congenital obliteration of the bile ducts.

(*g*) By cirrhosis of the liver leading to obstruction of ducts.

Hæmo-Hepatogenous Icterus.

Remember that in these cases we are dealing with, in the first place, increased blood destruction; in the second, some disturbance of the finer capillaries of the liver whereby the increased amount of bile formed from the dissociated hæmoglobin of the blood fails to pass out into the intestine, and becomes diffused through the lymph and blood. Examples of this form would seem to be present in the following conditions :—

1. Toxic, under the action of phosphorus, snake bite, arseniuretted hydrogen, toluylenediamin, pyrogallic acid, etc.

2. Acute Yellow Atrophy of the Liver.—While we are uncertain as to the exact cause of this disease, the changes that occur in the organ are identical with those seen in phosphorus poisoning, and by analogy we must suppose that here there is working some toxic substance producing this acute degeneration of the liver and the accompanying jaundice.

3. In Extensive Burns and Scalds.—More recent observations upon this subject by Hunter and others lead to the belief that not only does the burning of the tissue in itself lead to the great destruction of the corpuscles and liberation of their hæmoglobin, but also at the same time there pass into the blood certain toxic substances from the destroyed tissue which cause various disturbances, notably, necroses in the lymph glands (which necroses may possibly be the first step in the production of the duodenal and other intestinal ulcers occasionally met with); while again there appears to be set up a disturbance in the liver similar to that seen in poisoning by toluylenediamin.

There are one or two other changes concerning which it is not possible as yet to speak definitely; thus epidemic jaundice (Weil's Disease) ought probably to be included among the catarrhal and so among the hepatogenous group, as should also very possibly be certain forms of jaundice accompanying malaria. As to the jaundice of the new born (icterus neonatorum), that of yellow fever and that of pyæmia and of septic cases of icterus neona-

torum, these probably are hæmo-hepatogenous, though as I have already stated the slight tinge of the skin in septic disease may be due not so much to a true jaundice as to a staining of the tissues with derivatives of the absorbed hæmoglobin which have not yet been acted upon by the liver cells.

Icteroid Conditions—Urobilin Jaundice.

As already stated there is a class of cases in which the skin takes on more or less of a lemon yellow colour without their being evidences of bile pigment in the urine, and without the liver itself being profoundly affected, and it is probable that this pigmentation is due to no derivative of liver pigment, but is derived direct from changes occurring in the circulating blood. We see this lemon colour more especially in pernicious anæmia and in cancer, while a somewhat similar pigmentation accompanies some of the infective fevers. In pernicious anæmia, it has been found that the urine may contain a large quantity of pathological urobilin without a trace of bile pigment, and such urobilinuria has been noticed with increasing frequency of late years in various conditions, while at the present time it seems probable that icteroid conditions may be due to the circulation of such urobilin in the blood. Urobilin is a normal constituent in the urine; it is especially abundant in febrile urines, and, as Hunter has pointed out, wherever there is an excessive destruction of hæmoglobin unattended by hæmoglobinuria. Urobilin has been artificially prepared from the hæmatin of the blood and also by reduction from bilirubin. Miller has pointed out that intestinal micro-organisms possess the power of tranforming bilirubin into urobilin, and probably this is the ordinary mode of origin of the small quantities of urobilin which pass out with the urine normally. Thus the urobilin circulating in the blood when in excess and capable of tinging the tissues may be derived in two ways :—

1. As the product of destruction within the system (outside the liver).

2. As an absorption of converted bilirubin from the intestinal canal.

Most of the cases we have to deal with of slight yellowish pigmentation of the skin tissue would seem to be due to the former condition. It is quite possible that the unpleasant rather earthy yellow tinge of the skin of those suffering from chronic constipation is due to the latter cause.

XANTHOMA.

Another intrinsic pigment body is to be met with in a curious condition known as Xanthoma or Xanthelasma. In this condition there develop most frequently towards the inner canthus of the eye, but in advanced cases scattered through the skin of various parts of the body, and even in the mouth and elsewhere, small very slightly raised tumours of a curious yellow colour. In the majority of cases there is a relationship between this and hepatic disturbances, notably the presence of gall stones. Upon microscopical examination these tumours are found to contain a considerable number of large fat cells, which, instead of being colourless, contain diffused through the fat a bright yellow pigment. What is the nature of this pigment we do not as yet know, but the relationship to obstructive hepatic disorders would seem to indicate that it has some connection with the pigments of the bile.

MELANOSIS AND MELANÆMIA.

A pigment present normally in the body, which, however, is not related to the pigment of the blood, is that known as Melanin, This is granular and dark brown in colour, and situated within the cells, though sometimes it is found also free in the surrounding lymph channels. This is soluble in either alcohol and strong acids, and, according to Abel and Davis, who have recently published a very full study upon it, it is not primarily soluble in alkalies save under pressure at a temperature of 150° to 160°; it is peculiarly resistant to dilute nitric acid, and is present in 1 or 2 parts to the 1,000 in the dried epidermis of the negro; it contains no iron, and its ground substance appears to be a proteid holding a small amount of sulphur with it. In this presence of sulphur it

differs from bilirubin (and hæmatoidin). The iron-containing hæmoglobin holds 0.5 p.c. S., melanin 1.5 p.c. Normally this pigment is present in the Malpighian layer of the skin and again in the uvea and choroid of the eye. Apparently its use is to take up violet and chemically active rays, of light, to absorb the chemical energy of the sun's rays, and so to prevent inflammation of the more sensitive and vascular deeper layers. Pathologically this is found in abnormal quantities in certain pigmented (melanotic) new growths. It is also increased in amount in Addison's disease and in some cases of senile pigmentation. The melanotic sarcomata as a rule form very rapid metastases, and in some cases the amount of pigment developed in the cells of these growths is so great that the pigment circulates in the blood and leads to the condition of Melanosis, and is excreted by the kidneys. The urine in these cases is at first colourless, and gradually becomes brownish or almost black. Evidently there is a colourless precursor of melanin, which taking up oxygen becomes coloured. Thus it is generally held that in the cells of the skin some such chromogen is present, and that this is formed antecedent to the development of the pigment proper.

Pigmentation by Extrinsic Substances.

Minute foreign particles of insoluble nature may enter the tissues, and, becoming deposited there, may lead to pigmentation of the same. The most popular example is to be seen in *tattooing*, a process by which carbon, vermilion or other substances introduced into the skin, remain there, it may be for long years or for life, though there is in all cases some liability for the pigment to disappear, and the nearest lymph glands are found to contain the pigment particles. Similar pigmentation of the skin is to be found where, as a result of excoriation, dirt has been rubbed into the skin, or after the explosion of gunpowder in very close proximity to the surface of the body.

But the most extreme forms of extrinsic pigmentation are to be found in the lungs, in connection with various trades and occu-

pations which involve the inhalation of air charged with fine particles of mineral or even organic matter. These conditions are classed together under the term of *Pneumonokonioses.* Of these the commonest is the miner's lung—*Anthracosis ;* the stone mason's lung—(*Sillicosis* or *Chalicosis*, also found in glass grinders). *Siderosis*, where a metallic dust, more especially of the oxides of iron, becomes deposited in the lungs more especiallv of mirror polishers and again among knife grinders. And lastly in those working in porcelain factories there may develop the condition of *aluminosis* through the inhalation of clay.

Once these fine insoluble particles have passed the bronchioles and entered the air sacs, they gain a region where there are no cilia capable of passing them out and upwards to be expectorated. They set up a certain amount of irritation, and the leucocytes which are constantly passing through the epithelial lining of the air sacs act as phagocytes, take them up and now carry them into the lymph spaces of the lung tissue. Once here they may either be carried to the peribronchial lymph glands, or these leucocytes breaking down deposit pigment in the lymphatic vessels. A very favorite seat for this deposit is in the subpleural lymphatics, another in the connective tissue around the larger bronchi. As a result the organ becomes pigmented, and if the amount present be extreme, the irritation set up by these fine particles leads to the deposit of fibrous connective tissue around them, so that we find in the lung a generalised interstitial pneumonia with fibroid tubercles, in the centre of which are masses of the insoluble pigment, black in cases of anthracosis, reddish in the cases of iron, brownish in the cases of silicosis, etc.

Not only this but the mediastinal lymph glands are found densely filled with the pigment, and by the agency of the leucocytes this may travel to other parts of the body and be found in the interstitial tissue of the liver, kidney, etc. And here again in rare cases it may lead to a considerable development of fibrous tissue. Welch has described a very advanced case of *cirrhosis anthracotica* in the liver of a coal miner.

Other cases of pigmentation are brought about by the chemical changes occurring in metallic compounds taken up in a soluble condition from the intestinal tract. A well-known example of such a condition is to be seen in the blue line along the gums in cases of lead poisoning. The lead is taken in a soluble form, circulates through the capillaries, passes with the serum into the lymph, and in regions like the bases of the teeth, where a certain amount of fermentation is going on and sulphuretted hydrogen is being produced, the lead may be precipitated as a sulphide, and so bring about the bluish color of the gums. Similarly where large quantities of silver nitrate have been taken, the salt may undergo decomposition and the metallic silver is deposited in the lower layers of the skin, in the glomeruli of the kidneys, etc. This condition is known as *Argyria*, and those affected by it have a bluish and unearthly look.

Many other colored soluble substances taken into the system are excreted in the urine and cause abnormal coloration of the same. (Vide text book upon clinical examination of urine,)

Calcareous Degeneration.

The blood, lymph and tissues of the body all contain, normally, lime salts, and this being the case, it is evident that if these lime salts be deposited in the tissue, that deposit may be due to either, (1) a precipitation or deposit of the lime already contained in that tissue, (2) a precipitation of the lime brought to the tissue by the blood and lymph; or, (3) a precipitation of lime salts present, not in normal, but in abnormal amounts in the blood and the lymph. The salts thus deposited are, in the main, the carbonate and phosphate of lime, together with some magnesium salts. What are the conditions under which normally these salts are precipitated and deposited is a little difficult to state; we are not, that is to say, absolutely sure as yet as to the exact process whereby salts at one time soluble in the blood become insoluble and so precipitated. One class of cases possibly we can understand, namely, those cases which are seen in old people, and again in osteomalacia, in which, under some rather obscure conditions, the bone becomes absorbed and rarefied. We can see that in such cases the blood and lymph must become overcharged with the salts, and that may readily be precipitated in regions like the kidney, where, through excretion, the character of the blood becomes altered. But granting this, we are still left with the difficulty of apprehending how it is that normally in certain specific regions, *e.g.*, in bone, there is a precipitation of these salts. The most simple explanation is that there is possibly in the regions where these salts are precipitated a liberation of some substance which forms insoluble compounds of these salts; what that substance is there is considerable debate.

We may, in the first place, distinguish between physiological deposit or *ossification*, *i.e.*, infiltration of calcareous salts as an essential part of the process of new formation of tissue, and calcareous infiltration or *petrifaction*, in which no new tissue

is formed. In the latter case, we find that the process, save in the one case already mentioned, in which there is an excessive amount of salts in solution, is to be found characteristically in areas in which the tissue is dead or dying. Examples:—

1. Where there is the accumulation of excreted material, thrown off cells, etc. In a duct. we find that this debris becomes infiltrated with lime salts, *e.g.*, *rhinoliths* in the nose, *broncholiths* in bronchi, *phleboliths* in veins after thrombosis, salivary calculi in salivary ducts, pancreatic calculi, lachrymal calculi, etc.

2. *Lithopedion* or the petrifaction of the dead fœtus either in the uterine cavity or in the abdominal cavity (in extra uterine fœtation).

3. *Calcified Tubercles.*—As a result of the tubercular new growth, necrosis and caseation take place in the tubercular mass, and this caseous material becomes infiltrated with lime salts. The same process may also occur in gummata.

4. Calcification of tumours or portions of tumours which have lost their blood supply and undergone necrosis.

5. *Atheroma.*—Here with the hyaline degeneration and subsequent complete necrosis and liquefaction of the thickened arterial wall, there follows a deposit of calcareous salts and the formation of calcareous or atheromatous plates in the vessel wall.

It will be noticed that we have to deal in all these cases with a dead or dying tissue in which the process occurs. What happens in these cases, then, is that the circulating lymph containing soluble lime salts, those salts becomes precipitated. The probability is that these reach the region as soluble phosphates of lime and soda, and that here the nascent CO_2 given off by the tissue brings about a deposit of insoluble phosphates and carbonates. It has been suggested, however, that the process is not quite so simple, and that what occurs is a union of the lime salts in the first place with the fats present in the degenerated areas, leading to the formation of lime soaps which then undergo transformation. Woodhead and Irvine have attempted to obtain some knowledge of the physiological formation of the egg shell they found that hens kept without lime

salts soon cease to lay, and that, whether the animals be fed upon sulphates or carbonates of lime, the shell is formed of a large part of the carbonate of lime; there must therefore be conversion of sulphate into carbonate, and they found that the epithelium of the oviduct is in a state of great functional activity, and is full of granules of carbonate. They obtained still better results and still thicker egg shells upon feeding the animals upon phosphate of lime. In either case what happens is that the soluble salt is brought to the cell and there broken down, and the CO_2 present combines with the calcium of these salts to form the carbonate.

The proportion of carbonate to phosphate in various calcareous deposits varies greatly, in general the phosphate is greatly in excess. In bone the proportion is from 6 p.c. to 10 p.c. of carbonate, 50 p.c. to 60 p.c. of phosphate.

Atheromatous Degeneration.

A form of degeneration which frequently leads to calcareous infiltration is that known as atheroma. The feature in this is that the degeneration area instead of becoming smaller becomes larger; what appears at first as a connective tissue growth, gives way to a form of hyaline degeneration. Following upon the hyaline degeneration, the dying tissue disintegrates, becomes finely granular, and softened cholesterin crystals are present as well as the result of decomposition, and next, as already stated, in this softened and porridgy dead tissue appears a deposit of calcareous matter.

Calculi.

Vesical Calculi.—In the urinary passages, and more especially in the pelvis of the kidney and in the urinary bladder, it frequently happens that certain constituents of the urine are deposited in a solid form. There are many such constituents which may be so deposited. The following may be mentioned:—

(*a*) *Uratic* calculi, consisting either of pure uric acid or a mixture of this with urates.

(*b*) Calculi of *calcium oxalate.*

(*c*) *Phosphatic* calculi, consisting either in the main of triple phosphate (these are the more common), or of pure calcium phosphate (which are distinctly rare).

These are the most common forms, but in addition we also recognize the following: calcium carbonate, cystin, xanthin, sulphate of lime (two cases on record), silicates (in the bladder and urethra of the ox), guanin (in cattle), and fibrin (in cases of hematuria). The conditions under which these various forms develop vary somewhat both according to the condition of the urinary passages and according to the general metabolism of the body, but before passing on to discuss the various forms a few words may be said with regard to the general nature of urinary caculi.

In the first place, the salts composing these stones are never precipitated in a pure state, or, more correctly, they do not present their typical crystalline form, and if the salts be dissolved out it is found that there remains a matrix of mucinous material. We are not dealing, then, with a simple precipitation of the salts, but with the precipitation which occurs in a mucinous matrix. This is interesting, inasmuch as it has been found by experiment that if proteid matter, like white of egg, be added to the solution of calcareous salts, there is a peculiar liability for precipitation to occur in the colloid or mucilaginous white of egg. And this again indicates that for the production of stone it is necessary that there be some disturbance in the urinary passages, whereby there is a pouring out of a catarrhal or mucinous secretion. In the absence, then, of inflammation it would appear that we do not obtain the development of these calculi. In the second place, granting that we have such inflammation, the nature of the salt precipitated varies, mainly according to the amount in that salt or substance excreted in the urine, but also, markedly, according to the alkalinity or acidity of the urine. Thus in highly acid urine we are more likely to have a precipitation of uric acid and of oxalates, in the alkaline urine to have phosphates deposited. It follows from this that inasmuch as the stone is laid down in successive layers round the central nucleus, the composi-

tion of the successive layers tends to vary, and indeed we may have, and very frequently do have, a uric acid stone formed in acid urine, surrounded by deposits of the triple phosphates which have been formed in the alkaline urine.

The rarer forms of stone, like the cystin, guanin, xanthin, etc., depend upon the modified metabolism, whereby, instead of urates, these other nitrogenous compounds are excreted in considerable quantities, and so become precipitated.

URATIC CALCULI.

This may be divided into the pure uric acid calculi, which for the most part are small, hard and reddish or yellowish-brown in colour, and calculi of sodium and mixed urates, Na, Ca, NH_5, or Mg (the first of these predominating). These are looser in texture and less homogeneous, and are often associated with calcium oxalates. The conditions under which these calculi are formed is a matter of some little interest. Uric acid, which is a most insoluble substance, is a normal constituent of the urine in man, and in the bird is the one nitrogenous crystalline body appearing in the urine. It is a singularly insoluble body, and the question is, how does it, being insoluble, appear in the urine? As Sir Wm. Roberts has pointed out, it is not passed out from the kidneys and does not primarily appear in the urine in this insoluble form, but is excreted originally as a more soluble body, the so-called *quadri-urate*. Uric acid is bibasic, containing two atoms of replaceable H, and so it can form two series of salts, the neutral, which we can represent as M_2U, and the acid which we may call HMU (the M standing for the base, the U for C_5, H_2, N_4, and O_3). Now, the neutral urates are very unstable and may be left out of account; the acid salts or bi-urates are more stable, and it is in this form apparently that the urates are present in the tissues in gout. But the amorphous urates we find as urinary sediment are formed of neither of these salts. There is a third form, quadri-urates, already referred to. If one takes the uratic sediment of an acid urine, filters off the urine and places a little of

the sediment in a drop of water under the microscope, in the course of an hour or so it breaks up, and uric acid crystals are formed; while working on a larger scale, one finds that now the water contains in solution a true acid salt, the sodium bi-urate. Evidently, therefore, amorphous urates consist of a compound of uric acid with sodium bi-urate, a form which is moderately soluble, which may be represented as H_2U, MHU, quadri-urate. This substance is very unstable; it is most stable in normal acid urine, but even in this if the urine be only kept long enough it breaks down and there is a deposit of uric acid crystals. Apparently this deposit in these cases is due to interaction between the quadri-urate and the phosphates present. In the normal body this reaction would take a long time, but under certain conditions it may proceed more rapidly. The main condition is, lack of alkalies, and it would seem especially of sodium chlorides. Thus it is in fevers, in which there is a great diminution in Na Cl, that we get the most abundant deposits of urates. On the other hand, excessive acidity of the urine leads to the same result. Such excessive acidity is brought about by rich diet, and it is in the excessively acid urines that uric acid stone formation most frequently occurs. Thus, then, it would appear that if we have a very acid urine, and, associated with this, some slight catarrh of the urinary tracts leading to the excretion of mucus or broken down cells, we have the condition favoring the first development of a uric acid calculus.

The urates, especially ammonium urate, are deposited where there is alkaline fermentation in the bladder.

Oxalate Calculi and Oxaluria.

The oxalate of lime forms a frequent deposit in the urine both in health and in disease leading to the appearance of the familiar envelope and dumb-bell shaped crystals. The significance of this precipitation of the calcium oxalate has been a matter of much dispute, and it cannot be said that we as yet have at all satisfactory ideas upon the subject. Some consider the oxalic acid as a deriv-

itive of uric acid, while it is very evident that it appears in the urine when certain foods, such as rhubarb, tomatoes, etc., are taken in large quantities. These contain oxide of lime. But also a rich meat diet will lead to the increased deposit of these crystals. Other authorities are of the idea that it is not in many cases excreted as such, but is one of the products of an inflammatory and fermentative condition in the urinary tract. In favor of this view is the observation made more than once, that calculi of the oxalate have been found in one kidney and uric acid calculi in another.

The pure oxalate of lime calculus is characteristic in appearance, forming a heavy mulberry-like mass, round or oval, and very hard with tuberose projections. On section the different laminæ have an irregular fortification-like appearance.

Phosphatic Calculi.

These next to the uric acid are the most frequent forms of calculus, while a very large number of other forms of vesical and renal calculi have a coating of the mixed phosphates. Their composition varies; softer forms which easily crumble are composed largely of ammonico magnesian phosphate together with phosphate of lime, with or without an admixure of carbonate of lime. Calculi of pure phosphate of lime are generally smaller and are dense and almost crystalline; these are relatively rare. The stones are relatively light, as already stated, with chalk-like appearance and fragile consistence. They are formed where there is ammoniacal fermentation of the urine. When the urine thus becomes alkaline, the phosphates already present are precipitated in combination with the ammonia which is evolved in the breaking down of the urea. The pure phosphate of lime is more probably formed where there is an alkaline condition of the urine without ammoniacal fermention.

The remaining forms of calculi are rare.

BILIARY CALCULI

Three main forms of gall stones are to be recognized:

1. Those formed of pure or almost pure cholesterin.

2. Those formed of varying admixtures of cholesterin and bilirubin calcium.

3. Those formed entirely of the bilirubin calcium.

The last form is rare, and is most frequently seen in the form of biliary sand within the ducts of the liver, or at most it forms small very irregular and almost mulberry-like calculous masses in the gall bladder. The mixed form is the most common, and in this the bilirubin calcium is mixed with varying quantities of cholesterin up to 25 . There may be small quantities of copper and traces of iron present. The general character of the *cholesterin* calculus is that it is pale yellowish, soft with a slightly nodular surface, and upon fracture it shows a radiate crystalization, the rays proceeding from the nucleus outwards. More rarely the calculi may be amorphous and of a more soapy character, not showing this crystalline arrangement. The *mixed* calculus is also of light weight, and may show frequently a more or less concentric arrangement of layers containing larger or smaller amounts of cholesterin; it varies in color from the deep red of bilirubin to the green of biliverdin.

FORMATION OF BILIARY CALCULI.—Cholesterin is a normal constituent of the bile, and it might be thought that the liver cells excreted it, but there is doubt concerning this. According to Naunyn's experiments, there is no marked increase in the cholesterin present in the bile after the administration of large quantities of this substance, and he concludes that it is not a specific product of the liver. On the other hand, the mucous membrane and the bile ducts constantly contain cholesterin, and as we have found here in Montreal in cases where there is obliteration of the cystic duct, we may have calculi of pure cholesterin in the gall bladder which has been completely cut off from the bile. The probability is that if there be sub-acute catarrhal inflammation of the mucous membrane of the gall bladder and bile ducts, there is an increased excretion of cholesterin, and with the douring off of

mucin we have the conditions set up favorable to the development of a cholesterin stone. With regard to bilirubin, it may be said that this in itself is never precipitated, but under certain conditions it is precipitated as an insoluble compound with calcium. Both bilirubin and calcium are normally constituents of the bile. Why the combination takes place of the two it is difficult to say; according to Naunyn, the presence of albuminous or mucinous material favors the combination. Here again we have to pass back to the catarrhal condition of the bile passages; it is this which in the main leads to the combination of the calcium and the bilirubin, and to the deposit of the same in the insoluble form. There are, however, apparently other favoring causes. We find that such stones are rare before 25 and most frequent in old age; that they are more than twice as often found in females as in males; that those leading sedentary lives are more liable to suffer from this stone than those leading active existence. So also those having long intervals between meals seem to be somewhat liable to the condition. Evidently, therefore, stagnation of the bile is an important predisposing cause. Possibly, this stagnation acts by permitting the alkaline bile salts to be re-absorbed, and thus the bile becomes more acid, and this acidity is favorable to the deposits of the salts. But the stagnation may act in another way, by leading to irritation and to slight chronic catarrh, and in the stagnant bile, as recent observers have shown, certain bacteria, notably the colon bacillus and the typhoid bacillus, may be found, and probably these lead directly to slight inflammatory conditions of the part. The quality of this inflammation and the position would seem largely to determine whether cholesterin or pure bile pigment deposit takes place.

Most frequently we have to deal with a few stones, three or four; we rarely meet with a single large stone; not infrequently we come across large numbers of small facetted mixed stone filling up the gall bladder. Otto has described a case in which he counted as many as 7802. The nucleus of the stone consists most often of mucus with bilirubin calcium; sometimes a foreign body forms the nucleus, a round worm or needle, or other minute body.

Necrobiosis and Necrosis.

It will have been seen in the preceding lectures that there is considerable difficulty in not a few cases in determining whether what we speak of under the broad term of degenerations are not some of them more truly to be described as localised necroses; that is to say, in many cases of hyaline degeneration, for example, and in conditions of calcareous infiltration, what we have to deal with is a series of changes occurring in tissues which have been cut off from the blood supply and have died, and the changes here mentioned are changes occurring in tissue that has undergone local death. Thinking over this matter it will be seen that it is difficult to make out, in some cases at least, at what point death intervenes. In other cases it will be recognized that the death of the tissue is a sharply defined event; there can be no doubt as to the loss of vitality in the limb, for instance, when the blood supply is cut off. Thus it is useful to distinguish between the two conditions of *necrobiosis* and *necrosis*.

NECROBIOSIS.—I have already mentioned some conditions of necrobiosis, namely, the hyaline and calcareous degenerations or infiltrations. Other forms about which a few words should be said are, the later stage of fatty degeneration and caseation, as also a condition already mentioned, namely, the later stages of atheromatous degeneration.

In the condition of *caseation* we have to deal with transformation of the tissue into cheesy-like material. Such change is seen more especially in tubercular and syphilitic foci of disease and in some new growths. In all cases where we have such caseation, we have a cutting off of an area from its blood supply, and this produces what we may term as "slow death of the tissue." So far as this can be followed, what happens in the first place is that the cells die and the nuclei lose their power of staining. Possibly before this the cells have undergone to a certain extent albuminous and

fatty degeneration ; but next, the cells disintegrate completely, the fibres, if any are present in the area, become broken down and disorganised, and what is left is a finely granular debris, in part albuminous, in part fatty, and this becomes more and more inspissated through the absorption of fluid from the area. Unlike cheese proper, this material, while containing fatty globules, does not contain a very large proportion. According to Hauser and others, this caseation corresponds in many points with the process of disintegration which sets in when fresh tissues are removed aseptically and preserved in sterilised tubes at the body temperature. It seems to be a process of the breaking up of the albuminous bodies of the tissues into their most closely related decomposition products.

(For a note upon Atheroma see *ante*.)

NECROSIS.—By necrosis we mean the local death of the tissue apart from the death of the rest of the body, and while in its broad sense the term includes all forms of local death, in its finer sense we distinguish between the necrobiosis or gradual death of a tissue preceded by degenerative changes, and necrosis, or sudden death not so preceded. The symptoms of this local death are difficult to define. In many cases we recognize the death by the fact that the nuclei of the part lose their power of staining, but it is familiar to all of you that parts may be cut off from the living body by the surgeon, or may be removed from the dead body in the post mortem room, and that those parts are certainly dead tissue and yet the nuclei may continue to stain well ; so that lack of staining of the nuclei is not a sufficient indication : in short, without further discussion it may be said that we are wholly wanting in chemical or micro-chemical or histological tests whereby to distinguish whether the cell is alive or dead. It is only some little time after death that we are able (and then not always) to make sure that a given cell is dead. Still, as in so many other cases in which it is impossible for us to give any exact definition, we have a general appreciation of the existence of such local or general death of tissue. In some cases the changes occurring after death of a tissue

or part are very well defined; we can distinguish thus the conditions of mummefaction or dry gangrene, sphacelus or moist gangrene, coagulation necrosis and the actual cell destruction which occurs in burns and severe injuries.

Dry Gangrene.

In mummefaction or dry gangrene, the dead tissue becomes hard, dried up and brownish black in color. Such dry gangrene can only occur in conditions in which there is arrest of the arterial supply to the parts, together with little or no regurgitation into the vessels of venous blood. It depends upon the evaporation from the tissues, and thus can only occur in the exposed parts, notably in the extremities of the limbs. There may be a preliminary stage in which the part is somewhat swollen with the presence of vesicles and bullæ upon the skin, but as these burst and lose their fluid, evaporation takes the upper hand, and gradually, without any marked fermentation or putrefactive changes in the tissue, all the tissue elements become dried up and shrivelled.

Moist Gangrene.

Moist gangrene on the other hand is due to either continued passage of certain amounts of blood to a part through the arteries, or—a matter of more importance—to the regurgitation and backward passage of blood through the veins of a part, so that the dead tissue becomes in the first place greatly congested and somewhat dropsical through the congestion, and then in this dead and moist tissue putrefactive micro-organisms make their way usually from the surface, where also there may be bullæ and breaking down of the outer layers of the skin. These putrefactive micro-organisms entering the dead tissue frequently tend to produce gas at the same time that they dissolve up the proteid matters. Thus the part becomes emphysematous, and, as usual in putrefactive processes, extremely foul. It should be noted here that in hospital gangrene, and again in certain cases of infection by the bacillus aerogenes capsulatus and more rarely by the bacterium coli, there may be a progres-

sive rapid death of the tissue caused by the infective agent, with abundant development of gas. With this breaking down, or even preceding this, the blood corpuscles within the vessel may lead in their death to diffusion of their hæmoglobin, and the part becomes discolored, and the discoloration is further increased by the formation of sulphide of iron through the interaction between the H_2S present and the iron of the hæmoglobin and tissues. In this way, with there being numerous chemical changes and forms of decomposition at work, the softer tissues are gradually dissolved up, the bones being the last to be acted upon.

In both dry and moist gangrene while these changes are occurring, at the edge separating the dead from the living tissue there is set up a zone of inflammatory change, and there is developed a *zone of demarcation* thus between the dead and the living tissue. According to the condition of the individual and the virulence of the microbes which gain entrance into the dead part, and, thirdly, according to the extent of the dead tissue, so do we either have this zone of demarcation well developed as the first stage of the process of the cutting off of the living from the dead tissue, or we have it ineffectual, and the process of tissue death extends gradually. With the absorption of the toxic products, and it may be also of septic micro-organisms from the dead area, the death of the individual intervenes.

Coagulation Necrosis.

This term was given by Weigert to one of the earliest changes which occurs in the death of tissues. If a part be deprived of its blood supply in the absence of any microbic disturbance the cells undergo a somewhat characteristic series of changes. This is well seen in the first stage of white infarct. The part becomes firm and homogeneous, and upon microscopic examination it is seen that the boundaries of the individual cells become indefinite, and the nuclei of those cells have lost their power of taking up stain, their chromatin has disappeared. With this the whole tissues under the microscope have a glairy or somewhat

hyaline and homogeneous appearance. It would seem that the process which occurs here is one very similar to that which occurs in musclein rigor mortis. There is a process of coagulation of the soluble proteids of the tissue cells so that they become fixed or rigid, and it has been suggested that the change is due to a liberation of a ferment acting in a similar manner to the fibrin ferment of the blood, so that this process of tissue coagulation is held to correspond to the process of coagulation of the blood. In such coagulation necrosis, it is not only the cells but the intercellular substance which undergoes this change, so that, as above stated, the whole area becomes verged into a more solid mass.

Death of the Individual.

Much might be said about the process of death, but here one can only record a few of the more important facts which have to be taken into account. I have already pointed out to you that during the course of life the various tissues undergo in turn a condition of atrophy and removal, and thus inevitably there comes a period at which, through want of equilibrium and want of capacity on the part of the remaining tissues, the vital functions can no longer be properly performed; thus naturally, through this imperfect performance of those functions, the time comes when, through their exhaustion, what we term *physiological* death ensues. Such physiological death, or the imperceptible sinking out of existence, is relatively rare; generally at the end of a healthy life, from the lowered vitality of the tissues, some infective agent gains a hold upon the tissues, and the disturbances set up by this are the direct cause of death. More often the individual dies at a period at which, save for the intervention of some external agency or some process of disease, the tissues of the organism are still capable of sustaining life for a considerable period.

There are, it is needless to say, many external influences which must inevitably bring about cessation of life. Traumatic disturbances, such as explosions and tearing to pieces by mach-

inery, naturally bring about this condition, but in addition we may state that practically all those conditions which will cause disease of the body may cause death.

However brought about, we recognize this condition of death by the cessation of the functions of the different systems. Usually, though not always, there are three main systems, arrest of activity of which inevitably leads to this condition, namely, the respiratory, circulatory and the central nervous systems, and we can in general ascribe the immediate cause of death to disturbances occurring in one of these three. In the majority of cases we find that respiration ceases first, but if we enquire further we see that the cessation is due to the stoppage of action of the respiratory centres in the medulla, so that death is in most cases really due to cerebral failure. But there may be primary respiratory death, as in suffocation, just as there may be primary cardiac death seen in rupture of the heart, or again after the action of certain poisons upon the heart muscle.

We recognize death by the complete cessation of the respiratory movements and next of the pulse, and again by the loss of the finer reflexes, notably of the muscular reflexes of the eye. Often, however, the muscles and the peripheral nerves remain capable of stimulation for some little time after the heart and the lungs have ceased to act. Next, the skin becomes pale and the body becomes cold, though occasionally there has been observed a post-mortem increase of temperature. In a varying time the muscles become rigid (rigor mortis), the rigidity being due to the coagulation of the muscle proteid or myosin. The time for this coagulation varies greatly. Fuller details concerning this and concerning the development of post mortem lividity are given in text-books of Legal Medicine.

On the Effects of Disease on One Organ or System of the Body Upon the Rest of the Organism.

We now pass on to another branch of General Pathology, one which has been too much neglected, which, considering that General Pathology is the study of the diseased conditions and the general scientific study of disease and its manifestations, is of the highest importance. Indeed a knowledge of the relationship between the local diseases and general systemic disturbances is the basis of successful diagnosis and prognosis.

In the lower unicellular animals and plants each individual cell is a separate individual, and if one or many cells in any colonial form, as, for example, one of the *Myxomycetes*, be removed, not only can these continue to exist, but the colony of which they form a part is in no wise disturbed by their removal. As we pass to the simpler Metazoa, we find that there is separation and distribution of function between the different cells forming the individual. Those which are external become more especially protective or motor, or charged with the functions of obtaining food. Those which are more internal gain digestive or reproductive properties, but in these lower forms the individual cells still retain the potentiality of taking on one or other function, so that if they be separated from the main body they can reproduce a complete individual. Where this is the case it is evident that the interdependence of different cells (and different tissues) is incomplete and imperfect, but as we ascend the chain of animal forms we find that this interdependence of one tissue upon another becomes more and more absolute, so that at last only one set of cells, the generative, is left which has the potentiality of independent and complete development into individual forms. The other cells cannot exist alone, and can only perform a very limited series of functions. A muscle cell,

of a vertebrate for example, depends for its continued vitality upon its connection with the nerve cell and the nutrition which is brought to it by the blood, and the nerve cell, while controlling the muscle cell, undergoes atrophy, if the muscle cells to which it is connected be destroyed ; while the blood exercises its functions largely through its cell contents, obtains the nutritive materials, which it holds, from the cells of various organs, by a process of excretion, and the condition of the blood depends upon the proper working of the cells of those organs. Thus, then, in man we find that the tissues and the cells of these tissues are wholly dependent upon the proper activity of the cells of the other tissues of the body, and we may lay down the rule that *anything which affects one tissue tends secondarily to have an influence upon the other tissues of the body and upon the system in general.* Thus, then, speaking broadly, disease of one organ not only disturbs that organ, but influences the system in general, and this disease tends not only to have local, but to have general effects. But while thus is the case, we have to recognize also the continual action of another biological law, that, namely, of Reserve Force.

RESERVE FORCE.—Briefly, there is no single tissue in the body which, under normal conditions, is exerting its maximum activity. Every tissue of the body may be said to be present in marked excess. Three-quarters of the liver may be removed from the rabbit, and the animal still remain apparently in perfect health; the whole spleen may be taken away from man or the dog without recognizable ill effects; 15/16ths of the pancreas can be removed without the immediate development of diabetes. Very many similar examples can be given ; indeed, upon the existence of this reserve force and of reserve material depends the vitality of such delicately constructed organisms, as man and living beings in general. We thus are introduced to this paradox that, *whereas every organ and every cell is interdependent upon the influences of every other organ or cell of the body, a large number of cells and a large proportion of any given tissue may be removed or rendered inactive without evident and immediate disturbance of the rest of the organism.*

Such reserve force will manifest itself, or may be called into action in several ways. In the first place, any given organ may be quantitatively so developed as to possess in itself more cells than are requisite for the due performance of the normal functions of the body; or, secondly, and we see this best in paired organs, if one of a pair of organs is destroyed, the other is capable of performing all the functions previously performed by the pair; or, thirdly, if one organ be diseased or destroyed, another organ which normally performs slightly different functions may undertake to perform the duties of the diseased organ. An example of the first of these conditions is to be seen in the case of the liver; of the second in cases of extensive disease or destruction of one kidney or one lung, and of the third in the pituitary body when the thyroid undergoes atrophy.

Bearing these considerations in mind, it will be seen that we may have the two conditions, (1) of local disease presenting purely local manifestations, and (2), of local disease leading to well-marked general systemic disturbance. In other words, granting that one has a local injury of any organ, that local injury may not immediately show more than local effects. One may have a diseased condition of a tooth and yet be in apparently perfect general health. And yet in other cases local disease of a tooth may set up, especially through the nervous system, such severe disturbances that the whole system is depressed and affected. Disease of that tooth may, by preventing proper mastication, throw more work upon the stomach; and while ordinarily the stomach through its reserve force might easily accomplish the additional digestion required, yet it is possible that digestion might be incomplete, and so in the third place, with this imperfect digestion, the nutrition of the body as a whole might become modified.

But, on the whole, the more we consider the matter, the more we see that the existence of this reserve force is the main preventive of general systemic disease, and is capable of explaining why it is that i n the post-mortem room we may find individuals

presenting extraordinarily extensive disease of one or other organ which must have been present for months and for years, during which period the general health had not been so far affected as to prevent performance of the vital functions in general, or indeed to lead to recognizable symptoms during life.

But granting thus that there may be compensation for local disease, we must recognize that that local disease does have its influence upon the rest of the organism; life and the bodily functions are carried out, but they are carried out upon a slightly or greatly limited plane. A kidney hypertrophied in consequence of insufficiency of the other kidney is more susceptible to disease than the normal organ, and we must see generally that the organ presenting local disease works at a disadvantage. It may be said to have a certain amount of reserved force when diseased, it works at a level nearer to the limit of that reserved force, and thus any extra demand upon its action, to which normally it could easily reply, is apt to be too much for it, it expands imperfectly, and now general systemic disturbance ensues with comparative ease.

From these general considerations I would now pass on to consider the main systems and the main organs of the body, one after the other, and will attempt to point out the broad facts which bear upon the relationship between disease of these organs and systems and the rest of the body. I have already discussed at some little length the effects of changes in what some would term the circulating tissue of the body, namely, the Blood, and so would now first take up the effect of disturbances and disease of the organs of circulation, of the capillaries, arteries, heart and veins.

THE EFFECT OF DISEASED CONDITIONS OF THE HEART UPON THE SYSTEM IN GENERAL.

Immediately we begin to discuss this subject of relationship between one organ and the rest of the body, we are arrested by the fact that the disease of the organ may be a primary condition, or, as shown in the preceding paragraphs, may be a secondary

effect of disease in other parts of the body. It is at times easy to recognize that we are dealing with a primary and not with an induced condition, at other times it is very difficult to make the distinction ; nevertheless, clinically, it is a matter of the highest importance to attempt to do this, for it will readily be understood that treatment to be successful may have to be very different in primary and secondary disease. If cardiac disturbance is set up, for example, by continued peripheral resistance to the blood flow due to arterial disease, then the attempt to treat the heart condition directly will not only be unscientific, but will be likely to be without satisfactory result. What is needed in such a case is to endeavor to modify the condition of the arteries. Altogether, this distinction between the primary and the induced disease of the organ is too little regarded, and it might be well if, following certain French authorities, we made more distinction between the two states of disease, employing the term *disease* to indicate the primary condition, the term *affection* to include the secondary and induced distu rance.

Once the tissues of an organ have passed into a morbid state, it is clear to see that the disturbance in the organ itself and its working will proceed along the same lines, and the secondary disturbance that the morbid condition of the organ induces in other parts of the body will be of a like nature whether the disease be primary or secondary, with this one difference : in the latter case there will be superadded the disturbance and the symptoms due to the primary disease elsewhere. Bearing this in mind, it will be seen that in discussing, for example, the effects of disease of the heart upon the rest of the system, we must take into account both primary and secondary affections of the organ.

In order to discuss the effect of heart disease upon the rest of the body we must in the first place recognize what are the functions of the heart normally, so that we may be able to analyse and see along what lines disturbed action of the heart may lead to disordered conditions elsewhere. In the first place, we see then that the main function of the organ is to propel the blood through the

tissues of the body and to keep up a proper circulation. And, dealing now with most elementary matters we recognize immediately that anything which will hinder the heart in this, its primary function, will, by hindering the circulation, cause malnutrition of the various organs, will lower the vitality of the cells of the body and induce a series of conditions of atrophy and simple degeneration and impaired function.

We have then to analyse the work of the heart, and in so doing we see, in the first place, that it is a double acting pump. During diastole it may be regarded as a suction pump sucking in and receiving blood from the veins; during systole, it is a force pump forcing the blood through into the arteries. With Cohnheim, therefore, we must in the first place discuss the factors which disturb one or other of these functions, and the effects of such disturbance. Following upon this, we shall have to discuss other points arising out of the nature of the cardiac activity; conditions of hypertrophy, or dilatation, of rate of beat and so on.

The Heart as a Suction Pump.

Compared with the force exerted by the organ as a propulsive agent, the suction action of a heart is relatively feeble; nevertheless it is there, and, under normal conditions, the very act of relaxation of the contracted muscle of the right and of the left ventricles of necessity leads to the production of a lowered and negative pressure in the ventricular cavities, and as a consequence the blood flows in. This filling of the ventricles is due, then, in part to the suction action; it is due also at a later stage of the ventricular diastole to the active pressure of auricular contraction, so that the final portion of the ventricular filling is active and under the positive pressure of the contraction of the auricles. But the auricles themselves normally exercise relatively but a small pressure upon the blood during their contraction, so that the force acting to produce distension of the ventricle is under normal conditions very slight as compared with the forces requisite to eject the blood from the heart. And being comparatively slight it requires but a comparatively slight external disturbance in this por-

tion of the cardiac action to induce grave modifications in the circulation. If, for example, the pericardium becomes distended with fluid, that fluid pressing upon the auricles and the ventricles may without difficulty lead to so much hindrance to the expansion of these organs that a negative pressure in their chambers during diastole is wholly wanting, and even at a slightly greater external pressure the positive force through which, at certain periods of the cardiac and the respiratory cycle, blood is forced into the heart from the veins may be overcome. Thus we may have either a condition of obstruction to the entrance of blood into the heart and a blocking of the blood of the venous side of the heart with the development of passive congestion of the organs and all its attendant results, or, if the pressure be more extreme. the moment may come when practically no blood is able to enter the collapsed right auricle and ventricle, and at this moment sudden death must ensue.

These conditions may be induced experimentally. Taking a healthy dog with all necessary precautions of anæsthesis and of artificial respiration, the left side of the chest may be opened, a canula be fastened into the pericardial sac, manometers be brought into connection with an artery and a systemic vein (so as to determine the arterial and venous blood pressure respectively), and then the cardiac cavity can be gradually filled with some bland fluid like olive oil. When this is done, it is found that when the oil manometer attached to the pericardial sac indicates a pressure of 60 or 70 mm. there is a marked fall in the arterial pressure and an equally marked rise in the venous pressure. The tension in the pericardial sac can be raised and will then lead to more and more pronounced lowering of the arterial and rise of the venous pressure, until at last the pulse waves completely disappear from the arterial record ; that is to say no blood is entering the arteries from the heart and consequently there is none which can be propelled forward into the arteries and cause the pulse wave. If this pressure be kept up for more than a moment, death naturally ensues from stoppage of the circulation.

In conducting this experiment it has been noticed that when a certain moderate pressure has been brought to bear upon the exterior of the heart, and the arterial blood pressure has in consequence been impaired, if the heart be kept in this condition for a little while, the arterial pressure slowly but steadily rises, the venous pressure showing a corresponding fall. This observation is of direct interest clinically, for the explanation of the change is that the pericardial sac is elastic, and as it gradually expands under the distending forces of the contained fluid, the pressure exerted by that fluid upon the heart is reduced and the condition of the circulation necessarily improved.

Applying now these observations to the human heart, we find that any collection of fluid within the pericardium is liable to interfere with the circulation, lowering the arterial tension and tending to cause venous congestion. But it is remarkable at times how the cavity may contain several hundred ccm. of fluid without death being directly caused by it, while at other times from 150 to 200 cc. of fluid has evidently been the cause of sudden death (as in some cases of rupture of the ventricle). The explanation of this is that everything depends upon the rate at which the fluid collects in the cavity. If it collects slowly, as in tuberculous pericarditis and in some cases of hydropericardium, the parietes give way gradually before the constant slow exudation of fluid. If it is exuded rapidly, as in very acute pericarditis or in rupture, there is no time for this giving way, and the pressure within the sac rapidly increases until death ensues.

Other conditions leading to pressure upon the heart from without and to arrest of the suction pump action may here be mentioned :—such are intrathoracic tumours (extensive aneurisms, mediastinal growths), copious hydrothorax and pleuritic exudation.

The Heart as a Force Pump.

The main muscular activity of the heart is devoted to forcing the blood into the arteries. It is not necessary here to speak of the valvular mechanism whereby the blood normally only flows in

one direction, nor again is it necessary to do more than point out that in contracting upon the blood we almost of necessity are led to conclude that the shortening of the individual fibres is largely idio-muscular, that is to say, that it is directly dependent upon the stimulus afforded by the intracardiac pressure and the nutrition of the muscle through the coronary arteries, the nervous system having, according to recent very convincing experiments of Townsend Porter and others, very little to do with the initiation of the contraction, for the nerve fibrils passing to the muscle fibres are apparently in the main sensory. Thus the tip of the cat's heart in which the coronary circulation is still continued, but which is completely separated from the rest of the heart, will beat of its own accord. All the same it must not be forgotten that the central nervous system undoubtedly has a regulating power, regulating the heartbeat and apparently also the force of the contractions. Bearing these facts in mind it will be seen that the contraction of the heart primarily depends upon its proper nutrition, and that the first effects that we have to study are in connection with the blood supply through the coronary arteries, for if this be interfered with the work of the fibres is impaired, the contraction becomes weaker, the arterial pressure lower and the amount of blood thrown out from the heart diminished.

If we experimentally ligature a branch of the coronary artery, the heart in the course of a few seconds becomes irregular in its action, and in a large number of cases, within a minute, passes into a condition of vermicular contraction from which it rarely emerges. In such an experiment two points are brought out :—

1. That ligature of the coronary artery arrests the blood flow of one portion of the ventricular muscle, *i. e.*, the branches of the coronary artery are in the main terminal. Where ligature does not lead to death we must suppose that collateral circulation is developed and that the condition of the muscle fibres in the area recovers.

2. That there is some mechanism whereby disturbances of a portion of the heart muscle throws out of gear the working of the rest of the heart muscle.

Apparently the conditions brought about experimentally are seen in the conditions of angina pectoris. In this disease it is unnecessary to state that there is a sudden onset of intense cardiac anxiety and pain, which either may pass off or which may cause sudden or almost immediate death. In cases of true angina pectoris some disease is always found affecting the coronary arteries, in general a condition of sclerosis with endarteritis obliterans. Certain branches of the coronary artery are so much narrowed that if there be any extra exertion on the part of the heart the narrowing prevents a sufficient blood supply to the muscle of one or other region, and so soon as this is felt a condition of cramp or of intense cardiac pain is set up which may pass on to arrest of the heart action in general, and death. Similarly sudden death may be set up by embolism of one or more branches of the coronary artery. It is, however, to be noticed that sometimes the muscle fibres undergo an infarctous change (Myomalacia Cordis) without there being set up this generalised disturbance of the cardiac contractions; and again, that impoverished nutrition of the heart muscle may show itself as a generalised change with atrophy of the fibres, and (in cases of certain diseases, as for instance, diphtheria and pernicious anæmia) in a form of intense fatty degeneration, in some more chronic conditions in the form of a generalized replacement fibrosis. In any of these cases it goes without saying that the force of the heartbeat and the circulation in general becomes greatly enfeebled, and the weakened blood flow may lead to venous congestion and all its attendant disturbances. Other conditions affecting the heart muscle may be here mentioned in passing, as, for example, the presence of pyæmic abscesses in the muscle, the development of gummata, the growth of primary or secondary malignant tumours in the heart wall. All these conditions necessarily weaken the heart action and lead to constitutional disturbances.

Affections of the Endocardium of the Heart.

Of all portions of the heart the endocardium is that which shows the most evident disturbance, and here especially that por-

tion which from its position is subjected to the greatest strain and which is most liable to be affected, namely, that forming the different valves of the heart. That this is so is well shown by a comparison of fœtal and adult heart disease. In the fœtus it is the right heart that has the most work to perform, and as a consequence congenital heart disease shows itself especially on the right side. Such congenital valve disease would seem evidently to be the result of inflammation of the cusps during intra-uterine life. During adult life the left side of the heart has most work to perform, and diseases of the pulmonary and tricuspid valves are comparatively rare.

Valve disease appearing in later life is of three main classes; it is either (1) ulcerative, due to the invasion and growth upon the valves of pathogenic micro-organisms, or (2) is associated with acute rheumatism, and is here also inflammatory in nature but is not marked by such excessive lesions, though from the more chronic character of the condition the valves are the seat of great fibroid overgrowth, and as a consequence becomes thickened, while through the contraction of the fibrous tissue the orifices become greatly narrowed; (3) appearing later in life, valve disease is one of the manifestations of arterio-sclerosis. Here again the process is one of great fibroid thickening with contraction but with a greater tendency to degeneration in the new fibroid tissue, so that there are frequently calcareous deposits within the cusps. Another rarer causation of valve disease is actual trauma with rupture and loss of valve tissue through overstrain.

It is not easy to produce the conditions associated with valve disease by experimental methods, because the majority of conditions with which we have to deal in the human subject are of slow development, and the results of such disease are equally gradually developed. We can, however, obtain some knowledge of the results by experiments upon a dog's heart. Thus, if we put a ligature round the first part of the aorta and tighten this, we can reproduce some of the effects of *stenosis* or narrowing of the aortic valve; or again, by inserting a suitable rod into the carotid, we can,

by destroying in this way the aortic valves, reproduce some of the more important symptoms of aortic *incompetence*. The observations made in the first of these experiments are very instructive. If we draw a ligature round the aorta we can greatly reduce the diameter of that vessel and yet produce very slight effects upon the system in general; what we notice, if we place a manometer in connection, say, with the femoral artery, is that the peripheral blood pressure is maintained until the narrowing becomes very considerable, the only difference being that as the ligature becomes narrowed, the pulse becomes slowed. If we examine the heart under these conditions we see that it is contracting well and very forcibly, add to which that the left ventricle is distended. Whenever in fact there is any increased work thrown upon the heart the muscle becomes distended, just, in fact, as it is with the gastrocnemius of the frog. If a greater weight be attached to that muscle it becomes more elongated; so when there is increased resistance within the heart cavity there is a greater pull upon each individual fibre of the heart muscle, and the distension of the muscle necessarily results. Up to a certain point this distension of the left ventricle seems to improve the work of the heart. Just as we find with the frog's muscle, so here. The work of the frog's muscle is determined by the distance through which, in contraction, a weight is lifted multiplied by that weight, and it is not with the smallest weight that the greatest amount of work is performed. For instance that a load of 1-10th of a grm. a weight is lifted through 4 mm. and with a load of 1 grm. the weight is raised only 1 mm. Nevertheless the work done in the latter case is manifestly more than twice as much as in the former. In this way when the cardiac muscle has to work against increased resistance, even though the individual contractions be smaller, it may drive forwards an increased quantity of blood. With the increased resistance in front also the heart beats generally more slowly, there are less frequent but more forcible contractions. In this way, although the heart is called upon to do more work, it is able to do it because of the reserve force of the heart already mentioned, and the circulation is maintained in almost if not quite as good a state

as it was before the ligature. If now the ligature be drawn a little more tightly, then the limit of the reserve force of the heart is passed and it is unable to force the blood through the greatly narrowed aorta and signs of cardiac failure appear, the ventricle becomes greatly distended, each muscle fibre may be spoken of as being over-weighted, the contraction becomes very feeble, incapable of passing on the blood beyond the obstruction, the pressure in the arteries ligatured rapidly falls while on the other side of the heart one gets evidence of damming up of the blood in the veins, and if the condition be kept up death very rapidly ensues. We see a very similar condition of affairs in cases of aortic stenosis, and indeed of stenosis of any of the other orifices of the heart. A patient may for long years have an extreme degree of narrowing of one of these orifices, with well marked evidence in the form of a murmur as the blood passes through the narrowing. But for all these years that individual, if he does not over exert himself, remains with little evidence of secondary effects save in the heart itself. In the heart itself we have what is known as compensation, where, for example, there is narrowing of the aortic orifice, the left ventricle becomes hypertrophied and so becomes capable of contracting more forcibly.

As already stated, when speaking of reserve force and of hypertrophy, the overgrowth of an organ, in consequence of increased work, cannot go on indefinitely. With increased demand thrown upon an organ and increased work, it hypertrophies up to a certain point, but after this, if there still be a further demand thrown upon it, hypertrophy gives place to atrophy, to using up and exhaustion of the elements of the tissue. We do not know the laws which govern the growth of tissue sufficiently to be able to explain this limit to the growth of tissue. It may be that there is an intimate association between the proper working of the organ and the amount of blood supplied to it, that after a time the arteries, the coronary arteries in this case, are incapable of bringing sufficient nourishment. Certainly we find this, that in the young, speaking generally, hypertrophy is more extensive and compensation more

complete than in the old; in the young the arteries are more elastic and are more distensile than in after life. Thus it may be that this arrest of hypertrophy is associated with some incapacity on the part of the arteries to supply a sufficient amount of blood. In any case, hypertrophy of the ventricles is peculiarly liable to give place eventually to cardiac failure, and this may come on suddenly through some sudden strain, or more gradually through wasting of the hypertrophied muscle fibres.

CARDIAC HYPERTROPHY.

Here, in passing, a few words may be said as to the causes of cardiac hypertrophy. Hypertrophy being a response to increased work, we see that such increased use may be brought about in several ways:—

1. By difficulty to contraction of the muscle from outside, *e. g.*, in cases of chronic adhesive pericarditis where the heart has simply to expel the blood from the ventricle, but in addition has to pull the weight of the thickened and adherent pericardium with each contraction.

2. By resistance to the outflow of blood from the chambers. This resistance may be (*a*) endocardial, by disease causing narrowing of the valves. (*b*) Arterial, from increased arterial resistance. This is well seen in many cases of arterio-sclerosis and kidney disease, in short, wherever there is markedly increased arterial tension and increased difficulty in propelling the blood through the narrowed arteries.

3. By increase in the amount of blood which has to be expelled at each traction. Such increase may be (*a*) actual, *example* the beer drinker's heart, where apparently, from absorption of much fluid from the stomach, the vascular system for longer or shorter periods is in a condition of plethora. (*b*) Relative, where there is incompetence of the valves, so that at each systole the individual chambers of the heart have to expel not only the normal quantity of blood which reaches them in the ordinary course of

affairs, but in addition the amount which has regurgitated through the incompetence of the valve.

4. By functional or nervous disturbance, *e. g.*, hypertrophy of the heart in cases of tachycardia, seen well in cases of exophthalmic goitre. In these cases we recognize that through some nervous irritation the heart is called upon to beat more rapidly, and so far we do not recognize any lowering in the blood pressure which should explain this rapidity.

Here a few words may be said with regard to the innervation of the heart. While, as already stated, the heart muscle is capable of beating automatically and wholly apart from the central nervous system, and indeed, according to the best recent observers, wholly apart from the regulation of any peripheral sympathetic nerve cells situated in the heart itself, yet under ordinary conditions the beat of the heart and the work of the heart are regulated by the central nervous system. It is a matter of common observation that profound shock may cause great alteration in the rate of the heart beat, while experimentally we can discover at least two orders of nervous action upon the heart conveyed along two sets of nerves:

1. The fibres passing from the vagus nerve cause a slowing of the heart beat and a pouring out of a lessened quantity of blood in a given time, as shown by Professor Roy and myself. This diminution of the out-put may be as much as 30 or 35 per cent.

2. Accelerator, or, as we would term them, augmentor fibres coming through the sympathetic system, which, when stimulated, lead in general to increased rapidity of heart beat together with increase in the out-put of the heart.

Excitation of a mixed peripheral nerve, like the sciatic, usually produces effects on the heart similar in kind to those which follow direct excitation of the augmentors, but the phenomena are complicated by a greater rise of the pressure in the systemic arteries. Taking these facts into consideration, we can see that the vagus acts as a protective nerve to the heart, reducing the work thrown upon that organ, while the opposite is the case with the augmentor fibres.

Upon Dilatation of the Heart and its Effects.

As Tyson has pointed out, there are two conditions to be sharply distinguished one from another, which clinically and in experimental investigations are too often confused; these are the distension or expansion of the heart which constantly accompanies increased work, and the dilatation of the organ which is the indication of cardiac failure. As Roy and I have pointed out, whenever the heart has increased work to do and has an increased weight of blood to expel, the individual chambers inevitably hold larger quantities of blood. Under ordinary conditions, for instance, the ventricles practically become emptied with each systole; narrow the aorta or inject an increased quantity of fluid into the vessels, and in every case the heart enlarges, and this enlargement is not only during diastole and during expansion of the chambers, but is present also in systole. With increased work to do and with an increased weight to pull, as it were, the muscle fibres become more expanded when they are at rest, hence at the end of systole there is really some residual blood in the cavities. It follows from this that the mere enlargement of the heart is in no sense, in itself, an unfavorable sign. So long as there is a good pulse and good arterial tension, for so long such enlargement only indicates that the organ has undergone hypertrophy with its accompanying distension. If, however, there is a sudden great enlargement of the organ to be recognized, accompanied by irregularity of heart beat with enfeeblement of the individual beats and poor pulse, then we have indications that simple physiological expansion has given place to dilatation proper, and that there is the beginning of cardiac failure. Such dilatation may not only be the final stage of hypertrophy, but sometimes it develops suddenly from overwork, as for example in soldiers undergoing forced marches, and sometimes again, as pointed out by Graham Steele, alcohol causes acute dilatation of the organ, while probably also, as pointed out first by Roy and myself, and has more lately been shown by MacWilliam, the ill effects of chloroform are in part due to the development of a similar acute dilatation.

Upon Diseases of the Vessels and their Effects upon the System in General.

It is unnecessary for me here to point out that the quantity of blood contained in the vessels is far from sufficient to fill all the available space and to produce even a moderate tension of the vessel walls. Obviously if the blood is to flow with any considerable force through any part of such an imperfectly filled vascular system, this can be only brought about by the action of certain special mechanisms. That the elasticity of the arteries alone is incapable to maintain the arterial pressure at a high level is shown, as Cohnhein has pointed out, by the simple experiment of dividing the cervical cord or even the splanchnic nerve of the rabbit. Such operation cannot have profoundly modified the elasticity of the arterial walls, nevertheless there is at once an extreme fall in the blood pressure in the carotid artery.

It is specially a narrowing of the smaller arteries by the contraction of their circular muscular coats that brings in resistance to the escape of blood from the aorta and so leads to rise of the blood pressure. Indeed we must look upon the smaller arteries and the arterioles as being the main factors in modifying the arterial blood pressure. Once the blood passes this point, the resistance to be opposed in the capillaries with their very extensive sectional area, is comparatively trifling, and I am inclined to think that up to the present time the various writes and workers upon diseases of the arteries have too much neglected the changes in arterial resistance occurring in these smaller arteries. This contraction of the smaller arteries may be brought about in various ways; thus, the increased general arterial tension in dyspnœa would seem to be due to the direct action of the CO_2 in the more venous blood upon the circular muscles of these smaller arteries. Again, it is needless to say that the direct action of the nervous

system, more especially from the stimulation of the vaso-motor centre in the medulla oblongata, will bring about a similar contraction, and if a sufficient number of arteries are acted upon in this way, the general blood pressure must inevitably be raised.

The walls of the vessels are the most elastic of all the tissues, and in a large number of people they can bear the uninterrupted tension of the blood pressure during a long life without becoming overstretched or dilated. This property is accounted for by the presence of a muscular coat. If their elasticity be reduced the circulation of the blood is disturbed. Such reduction may be brought about by acute infectious disease, as typhoid and scarlet fever, chronic infectious disease, syphilis and tuberculosis and again by continued disturbance of general nutrition. Lastly, the overstrain brought about by the increased heart action may lead to similar results. In all these cases the walls of the arteries and veins become weakened and whether this weakening be or be not associated with actual organic change within them, their lumen dilates. As Thoma, to whom we are indebted for the best study of vascular disturbances, points out: if the capillaries remain unchanged, the mere dilatation of the arteries produces very little more than a lowered rapidity of the blood stream in the widened vessel. Also, though in this point I cannot wholly follow him, the simple act of retardation of the stream is the immediate cause of a new formation of connective tissue in the intima of the widened artery and by this new formation the lumen of the artery is now diminished and the latter is thus readapted to the blood stream. He, however, it must be confessed, has established this general law that where a vessel is enlarged or is larger than is necessary for the amount of blood passing through it, its lumen is reduced by the overgrowth of intima. This new growth of connective tissue renders the vessel less elastic and more rigid.

Increased rigidity of the wall means the increased resistance to the blood stream and in this way, in order to circulate the blood, the heart has to beat more strongly. Thus, in all the cases above referred to, whether there is from the first, increased activity of the heart or no, eventually thickening of the arterial wall leads to in-

creased blood pressure and thus in all these cases either primarily or secondarily, increased arterial tension is set up and as a first consequence of this we have the hypertrophy of the heart. Where these changes in the artery first appear, is a mooted point; we usually recognize them first in the large vessels but in some cases at least, and among these may be included, chronic alcoholism, syphilis and tuberculosis, careful histological examination would seem to show that the arteriols are earliest affected and in them we recognize the actual proliferation of the endothelium together with the connective tissue overgrowth of the intima; so that in these case the first morbid change would seem to be of the nature of an obstruction of the peripheral arteries due to endarteritis proliferans and to this may largely be ascribed the increased blood pressure and the dilatation of the larger arterioles which in its turn gives way to sclerotic and atheromatous changes in the same. Where these changes are produced in the arteries it is doubtful whether there is a coincident alteration in the elasticity of the capillary walls, but changes certainly do occur in the capillaries and the most noticeable of these specially where sclerosis is advanced, is a marked increase in their permeability and this in some cases leads to the development of capillary hæmorrhages, epistaxis, retinal, etc., more frequently it is the cause of serous effusion into the various parts of the body. Such effusions at first are transient and shifting, in the evening there may be œdematous swelling of the feet which during the night disappears and gives place to œdema of the eyelids; this in its turn disappears during the day. Obviously the change of the body and alteration in pressure due to position bring about these changes and the localisation of the œdema. Later the œdema of the lower extremities tends to become permanent and later other parts are affected; there are effusions into the serous cavities and multiple œdema or general œdema of the whole body is developed.

Ultimately the heart reaches the limit of its hypertrophy; it is unable to overcome the increasing resistance to the blood flow; there is heart failure and death ensues.

So far, what I have stated, refers entirely to the systemic

arteries. In the pulmonary arteries such sclerotic vascular disease is very slight and plays a very unimportant part. We rarely come across any advanced evidences of any advanced sclerosis of the pulmonary artery and at the same time dilatations or aneurisms of the pulmonary are great rarities. Both of these facts are associated with the further fact that the blood pressure in the pulmonary circulation is low. On the other hand there are several processes which do lead to increased resistance in the pulmonary vascular system. Among these we may mention induration of the lung tissue, ulceration and cavitation, emphysema, pleuritic exudation, pneumothorax, and again, everything which impedes the volume of the lungs, as, for example, pleural adhesions on the one hand and chronic bronchitis and blocking of the bronchi on the other. In some of these conditions we have actual obstruction to the onflow of blood either by pressure upon the arterial twigs or by atrophy of the same as in emphysema. In the other class of cases it must be noted that the flow of blood into and through the capillaries is normally largely promoted by the act of expansion of the lungs. In pleural adhesions there is only partial expansion, the gliding movement of the lungs towards the abdomen is rendered impossible, only the transverse diameter can be increased in inspiration.

Affection of the Veins.

With regard to the affection of the veins we know very little concerning general changes of these vessels, probably because such general venous disturbance is relatively rare. In some cases of general arterio-sclerosis it has been noticed that the venous wallsalso have been thickened, and even if this be the case, these vessels in general are so passive in their action that very little general disturbance will be caused except where such sclerotic thickening is extreme. More often we find that the venous circulation is acted upon secondarily. Whatever raises the intrathoracic pressure, whatever causes a positive pressure in the thorax must impede the emptyingof the veins. I shall speak more about this when I come to refer to the act of coughing.

Remember that where we have produced a condition of congestion of the veins and capillaries there is produced at the same time a favorable ground for increased exudation in consequence of increased permeability of the walls, and, as we see in inflammation, with this increased exudation of fluid, there will also occur increased migration of corpuscles both white, and in more severe cases red. So also there is produced a condition of impaired nutrition and functioning of the congested areas.

On the Disease of the Respiratory System and its Effects upon the System in General.

After the Heart and Circulation we naturally pass on to consider the Lungs, which indeed in their general isolated condition and their intimate relationship to the whole system present a curious parallelism to the heart. It is unnecessary here to enter into the physiology of respiration, although it must be remembered that a knowledge of the physiological functions and of the workings of these organs is absolutely essential to any comprehension of their action in diseased conditions. Like the heart, they possess a periodic action; unlike the heart, these periodic acts of inspiration and expiration are extrinsic and depend upon the surrounding musculature and this musculature has no automatic action of its own, but is controlled in the higher animals from centres in the medulla and the brain. There are two main controlling centres, the main respiratory centre in the medulla and the vagus centre which would appear to inhibit inspiration and lead to expiration, while at the same time the vagus filaments within the lung appear also to be sensory. It is the presence of CO_2 in the blood which would appear to largely stimulate the respiratory centre and lead to inspiration. Normally this stimulus induces regular inspiratory efforts (from 15 to 18 times per minute) and abnormally especially in febrile conditions and where the temperature of the blood is increased, the number of respiratory acts per minute may be greatly increased (up to 50 and more). Apparently also the centre may show evidences of diminished irritability or exhaustion; upon this theory the condition of Cheyne-Stokes breathing is usually explained. The centre in this condition is supposed not to react to the ordinary stimulus and when the blood has reached a certain point of oxygenation, it is said not to act; hence there may occur a pause of several seconds

in duration during which breathing ceases. Then with increased venosity of the blood the centre begins to act again feebly, gradually gaining in strength, and so there is a short ascending series of respiratory acts of increasing force, until through them the blood becomes so far oxygenated that now it ceases to stimulate sufficiently the centre and a second pause ensues.

But while there are these main centres there are also lower respiratory centres in the spinal cord or immediately controlling the muscles of respiration. Thus the diaphragm is innervated through the phrenie and the intercostal muscles through the branches of the dorsal nerves. Any disease or injury either directly affecting the muscles or these centres governing them, or again affecting the spinal cord between the main respiratory centre and the point where the respiratory nerves leave the cord, will profoundly modify the respiratory act by throwing these muscles out of gear. We rarely have paralysis of the diaphragm, more frequently especially in ascending spinal disease do we find the action of the intercostals arrested. It is possible thus to have either purely costal respiration or purely diaphragmatic, and if we have either one or the other in place of both, we obtain evidence that the system has some difficulty in gaining complete æration of the blood, that is to say, there is an obvious effort on the part of the muscles which remain in action.

Remembering then that the movements of the lungs and the passage into and out of them of air is dependent upon the mechanism of these external muscles and that both in health and disease this muscular nervous action has to be always before us, I would now pass on to discuss, in order, the various morbid conditions which may affect the lungs.

Just as in the heart we had first to consider the disturbances which might affect thc pericardial cavity, so here I would first take up the

Disturbances Affecting the Pleural Cavity.

Pneumothorax.—Normally through the absence of any air or fluid in these cavities the visceral pleura is in contact with the

parietal, and as the lungs are elastic and there can be no vacuum, these organs are always kept in a more or less expanded condition and the air sacs of which they are composed are, from the pressure of the atmospheric air entering through the trachea, kept more or less open. If, however, air is allowed to enter into the pleural cavity, then the pressure upon the lung, internal and external, is equalized, there is no force left to distend the air sacs and through their elasticity they undergo collapse. Such a condition of pneumothorax may be brought about in various ways:—

1. By external means through wounds in the chest wall. Note that the mere opening of the chest wall does not always cause collapse of the lung. While such opening brings the pressure of the external air to bear upon the organ, if the opening be small enough this opening is counteracted by the adhesion of visceral to parietal pleura caused by the existence of a thin layer of serum between the two.

2. By internal means through rupture of the lung. Most frequent causes of rupture are (a) traumatic, by a broken rib, etc. (b) by extension of tuberculosis and breaking down of lung substance through the pleura as also by gangreve of the lung, (c) by rupture of an emphysematous bulla.

3. Intrinsic, by the multiplication in the pleural cavity of some gas producin gbacilli, e. g., B. ærogenes capsulatus.

By all these means air or gases filling the pleural cavity cause collapse of the lung. If the other lung be unaffected, the two pleural cavities being separate, the one lung is adequate to serve the needs of the economy, and so long as it remains healthy for so long there is significantly little disturbance of general health.

Presence of Fluid in Pleural Cavity.

An accumulation of fluid in the pleural cavity has the same effect as that of air. As it accumulates, it presses upon the lung and causes its collapse. Such fluid may be, (1) of dropsical origin due in general to obstructive heart disease and causing a condition of hydrothorax. (2) Of inflammatory origin. Note that the most frequent cause of such pleurisy is tuberculosis especially in those

cases where the onset is insidious. It may, however, be also due to the extension of pneumococcus or other inflammations from the lung. There are also to be included the more purulent inflammation causing empyema as also the pleurisy accompanying cancerous and malignant diseases of the pleura.

Pleurisy and hydrothorax are frequently unilateral. Owing to the existence of the reserve force already mentioned, and to the fact that one lung can perform the work of two, these conditions are often overlooked because they produce so little general disturbance. Where both sides are involved the effect upon the general system by lessening the respiratory capacity of the partially collapsed lungs is very serious.

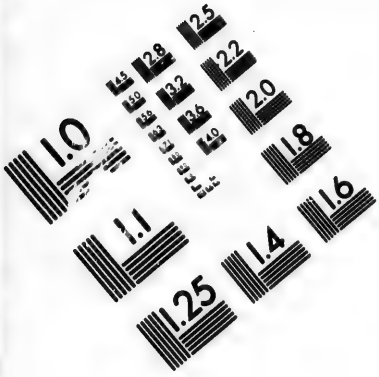
Other Causes of Collapse of the Lung.

A similar collapse of the lung may be brought about also by solid bodies filling up the pleural cavity as for example, mediastinal tumours, thoracic aneurisms, and on the left side conditions of greatly enlarged heart or of greatly distended pericardium. While also any body pressing from without upon one of the larger bronchi will have a similar effect.

Collapse may also be brought about from within the air passages. If anything blocks the bronchus so that the passage of air into the air sacs leading from it is stopped, then the air already present, both O. and N., is absorbed by the blood circulating through the walls in the sacs and tnere is a necessary collapse of these sacs ensues. A condition corresponding to that of collapse is that of fœtal atelectasis, the condition in which at birth the sacs have neveropened up and remain in their fœtal unexpanded condition.

Pleural Adhesions.

On the other hand the lungs may be permanently prevented from free movement and from possible collapse by the presence of inflammatory adhesions between them and the diaphragm. Where this is the case, frequently the inflammation extends down into the lung substance and the bands of fibrous tissue thus developed may in their contraction pull upon the bronchi causing their dilatation



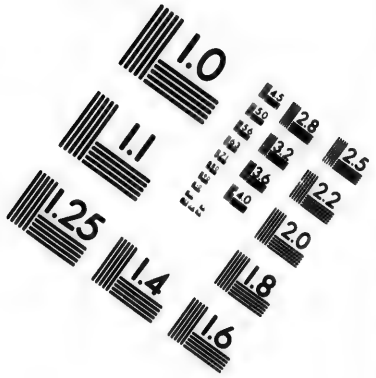
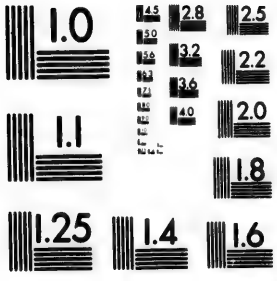
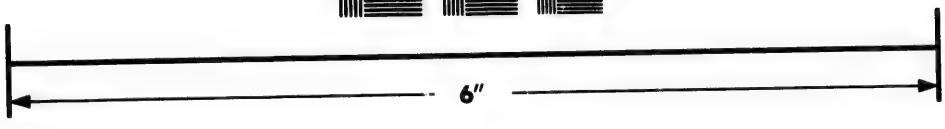
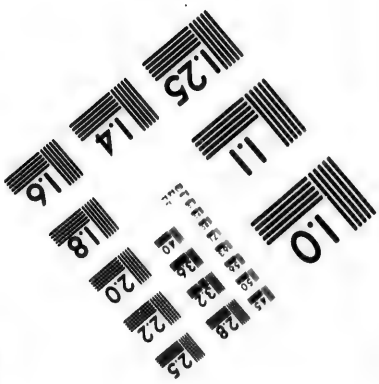


IMAGE EVALUATION TEST TARGET (MT-3)







Photographic Sciences Corporation

23 WEST MAIN STREET
WEBSTER, N.Y. 14580
(716) 872-4503

and thus in other ways pleural adhesions may lead to disturbed function in the lungs themselves.

Irregular action of the respiratory muscles are to be well seen in such conditions as coughing, sneezing, yawning, hiccough, crying, etc. Most of these are but temporary in their action and produce little general effect, though sometimes, especially in children, crying may lead to general disturbance, while continuous hiccough, such as occurs in hysteria and also again in uræmic disturbances, may lead to serious effects. In crying there are short deep inspirations with long expirations and a narrow glottis, relaxed facial muscles, secretion of tears often combined with plaintive inarticulate expressions. When crying is long continued sudden and spasmodic involuntary contractions of the diaphragm occur causing sobbing, and in addition the disturbed respiration may lead to considerable cyanosis.

Of these disturbed and irregular actions of the respiratory muscles, the most frequent and at times the most harmful to the system in general is coughing. Such coughing may be brought about by irritation of several portions of the respiratory tract as of other portions of the body, of the larynx, the hind wall of the trachea, the pleura, the spleen and liver, the stomach and even the uterus ; and the vagus seems to be the special nerve which more especially sets up the reflex act. There is in this act preliminary inspiration followed by closure of the glottis, sudden expiratory effort, compression of the air in the chest, and, the air being forced at high pressure through the upper air passages there is sudden opening of the larynx and what may be termed " pop-gun action." In a single act of coughing there is but little disturbance set up, but if the cough be frequent and more especially if it be paroxysmal it has its effect upon the lungs, the heart and the system in general. If the lungs be already weakened by inflammation, the blocking of the out-flow of the air coupled by the violent compression of the organs in the strong expiratory act, leads the pressure exerted upon the inner wall of the air sac to gravely affect its nutrition and so weakens the wall that it undergoes expansion and emphysema is the result. Similarly the bronchi may be more or less expanded

and bronchiectasis supervenes. It is very probable that in the production of these two conditions, a further factor at work is the fact that by the respiratory act certainly, portions of the lung substance are more directly compressed by the diaphragm and chest walls than are others so that certain parts are temporarily emptied and other portions are over filled.

The effects upon the circulation are also very evident. Owing to the action of the respiratory muscles, pressure is brought to bear upon the whole of the thoracic contents. The heart and great vessels are pressed upon and at first there may be actual rise of general arterial pressure and so if the arteries are weakened elsewhere at the beginning of the fit of coughing, there is some little danger of their giving way, e.g., of cerebral epilepsy, rupture of aneurism, etc. But if the cough be kept up, this same intra-thoracic pressure obstructs the return of blood to the heart and as a consequence we have cyanosis, dyspnœa, possibility of hæmorrhages from nose, conjunctival ecchymoses, etc.; what blood does enter the right heart finds increased difficulty in passing through the lungs in consequence of the compression to which they are subjected, and so there may be set up distension and hypertrophy of the organ. Thus coughing fits frequently repeated in those already weak lead to changes in the lungs, in the heart and in the system generally.

Parenthetically, note various kinds of coughs, the hard, dry cough in the first stage of acute bronchitis due apparently to the irritation of the mucous membrane of the bronchi and set up possibly by the pressure of the congested tissue upon the vagus nerve endings. As the mucous membrane pours off its mucus, this gives place to the fuller and deeper cough of the attempt to expel the mucus collected in the bronchial tubes. Note the ineffective cough of bronchiectasis associated with an attempt to expel the foul fluid which collects in the dilations to the bronchi. Evidently with bronchiectasis, the inner coats of the bronchi become modified and less sensitive so that they allow a considerable collection of fluid without any irritation being set up, whereas if the fluid continues to collect, at last it affects some region where the mucous mem-

brane is still sensitive and now the irritation causes the production of a fit of coughing. In chronic bronchitis with constant development of mucus, the cough is somewhat of the same nature as that of the later stages of acute bronchitis. In pneumonia in the early stage cough is not a prominent feature unless there be well-marked associated bronchitis. During resolution the cough is distinctly an effort to expel the softened material which blocks up the bronchioles and in pleurisy the sharp, painful cough is purely a reflex act due to irritation of the pleura. When effusion takes place the cough generally disappears or becomes less painful. Note that in phthisis the cough is purely of laryngeal origin and in other cases is brought about by the pouring into the bronchi of the products of broken down areas of the lung.

A word or two may be here said with regard to the sputum; remember that this varies in different conditions, from being thin and mucous with relatively few leucocytes to being muco-purulent as in bronchitis and broncho-pneumonia, or containing abundant leucocytes and red corpuscles as in the rusty sputum of pneumonia, or containing in addition actual cell tissue, elastic fibres, etc., as in cases of ulce rative phthisis and gangrene. In short the condition of the sputum is the most valuable diagnostic aid in determining the nature of lung disturbances.

Passing on to discuss the disturbances affecting the entrance of air into the lungs, this entrance of air into the lungs may be diminished or arrested by any obstruction to the free passage of air from the larynx downwards through the main bronchi and such obstruction may be either, foreign bodies within the air passages from inflammation and tumours affecting the walls of the air passages or from tumours pressing on these passages from without. In all cases the effects upon the system will be the same. Here note that save during the taking of food, and this very noticeably, in suckling children, disease of the nasal portion of the respiratory passages does not directly affect respiration, but remember that constant breathing through the mouth renders the lungs much more liable to disease. In the ethmoid plates and turbinated bones of the nostrils are mechanisms whereby the entering

air is warmed, is rendered moist and is freed from foreign particles; hence if these be thrown out of work, there is great liability for the lung to be irritated by the "raw" air which gains an entrance.

Obstruction to the entrance of air into the lungs leads to the various stages of dyspnœa and asphyxia and it would be well now to consider these.

DYSPNŒA.—Where there is any obstruction to the entrance of air into the lungs, the amount and pressure of the CO_2 in the lungs as a whole must be increased, the amount of oxygen diminished and as a consequence the blood must give up less CO_2 and take up less oxygen: as a result there is the characteristic feeling of dyspnœa, of air hunger. Increased CO_2 in the blood causes increased activity of the respiratory centre, the inspirations become more powerful and even the excessory respiratory muscles are called into play. As the external air cannot rapidly rush into the alveoli, the air in these becomes rarified and the upper portion of the chest may be pulled in by this means. If this condition of partial obstruction of the upper air passages lasts for weeks, there is hypertrophy of the inspiratory muscles; both inspiration and expiration are prolonged and breathing becomes slower.

Dyspnœa may be brought about whenever interchange in the gases is insufficient to satisfy the needs of the body. Such deficiency may be due to:

1. Obstruction in the air passages or lessening of the respiratory movements.

2. Extensive disease of the lung tissue so that there is diminished surface exposed to the air.

3. Deficiency of the oxygen in the air.

4. Impediment to the flow of blood through the capillaries.

5. Of nervous origin brought about by the disturbance of the respiratory centre. With this may be included heat dyspnœa in which condition the warmed blood acts as a stimulant to the respiratory centre.

Note great reserve force of lungs; there may be extensive tubercular and fibroid disease, or absolute destruction of whole of lung without dyspnœa showing itself, save on exertion.

Note on other hand frequency of dyspnœa secondary to cardiac disease; the dyspnœa of advanced emphysema; of pulmonary embolism, of pneumothorax; of acute bronchitis; of asthma.

Read up and study :—

Asphyxia, symptomes, nature and causes.

Asthma.

Inflammatory disturbances of the lungs, chronic and acute, regions affected results &c.

Disease of the Digestive Tract and its Effects upon the System in General.

We are apt rather to think that the mouth and the apparatus contained therein, plays only a minor part in the digestive process; nevertheless, we cannot but be struck by the very considerable emaciation and falling off of the system as a whole which accompanies any severe disturbance in this region of the body—thus it is certainly worth while to run over the main group of disorders affecting this region and their influence.

THE TEETH.—Note the important part played by the teeth in keeping up the general health of the body; the emaciation, etc. brought about by the imperfect mastication of food of those who have lost a number of teeth and the rapid return to the condition of well-being upon supplying such individuals with a satisfactory set of false teeth. A similar lowering of the nutrition may be brought about by any other condition leading to imperfect mastication, e.g. (1); inflammation and degeneration of the jaw bones, (2), Paresis or paralysis of the masseters and other muscles acting on the lower jaw, whether unilateral or bilateral, but especially the latter, and (3), inflammation or tumour of the parotid whereby these muscles are prevented from properly performing their work, or (4), ulceration, neoplasms and destruction of the tongue, whereby the passage of the food from side to side is rendered difficult, and so the whole of the food does not come under the grinding action of the teeth.

THE SALIVA.—While one is somewhat apt from one's physiological studies to regard the ferment—ptyalin—as the most important feature or component of the saliva, in so doing one is certainly mistaken. The ptyalin in the saliva is not very powerful and only acts for a very short time upon the food. Within a few minutes after the food enters the stomach, under normal condi-

tions, the action is arrested by the acid gastric juice.* The main function or functions of the saliva are not directly digestive, but are of an auxiliary or accessory nature. Secretion from the various mucous glands of the cheek, gums, tongue, etc., play a most important part in cleansing the mouth. The mouth is from its position exposed to the outer air and an admirable culture ground its warmth and moisture and the normal alkaline reaction of this for bacteria; secretion, seem all especially fitted to favour the growth of its bacteria, and thus if there be a little fluid in the mouth, and that be not frequently removed, bacteria multiply to an enormous extent. The continual pouring out of saliva prevents this multiplication; as bacteria grow on the surface, they are carried away, are swallowed, and the majority of them are destroyed by the acid gastric juice. Little time thus is given then to multiply and to set up disturbances. The saliva itself is but slightly bactericidal in its properties. It must, however, be remembered that there are other means whereby bacteria tend to be destroyed. Thus, constantly there pass out from the surface epithelium numerous leucocytes which, as a sample preparation of a film of saliva shows, act as scavengers on the surface of the buccal epitheplium, ingesting and destroying the bacteria.

Thus, alterations in the amount of saliva excreted and alteration in the constitution of the saliva, may not only cause local disturbance but have a general influence upon the system at large.

Alterations in Amount.

Hypersecretion—Ptyalism. Such hypersecretion beyond causing discomfort to the individual, does not so far appear to lead to very grave general disturbances, though possibly where the saliva remains alkaline, the amount of this alkaline fluid which passes into the stomach, may impair the action of the gastric juice by neutralising its acidity. We find this occurring as a reflex act; at the mere sight of food in the hungry individual; not unfrequently

* Certain recent observations have thereon some doubt upon this statement; it has been shown by skiagrams that the food remains for some little time at the cardiac end of the stomach, as in a pouch, and du ing much of this period the salivary secretion may continue to act npon it.

in pregnancy, and again in cases of gastric ulcer. In such cases of gastric ulcer there is frequently an increased acidity and pouring out of the gastric juice, and this increased pouring out of the saliva appears to be sympathetic, and possibly may be of some little good in neutralizing the juice.

Diminished Secretion.

This occurs in a variety of conditions and may aid greatly in establishing a greatly lowered condition of the system. Where there is a relatively dry mouth, and the cleansing process is arrested, not only does mastication and deglutition becomedifficult but bacteria find their way into the buccal cavity, grow upon the surface of the tongue, gums, etc., set up fermentative processes, cause foul breath and from their abundance they may be taken up by the breath, and so set up secondary inflammatory process in the lungs, and even though the majority may be only mildly virulent they may by their abundance and the abundance of the products excreted by them, lead to destruction of the surface epithelium and the formation of ulcers, production of hæmorrhages, etc., etc. We find such diminution in certain febrile and infectious conditions notably in typhoid and pneumonia. The dry dirty brown tongue of typhoid owes its main features to this lack of salivary secretion, although, as I shall point out later, the condition of the tongue in many cases is in part determined by the other portions of the digestive tract. Inflammation or disturbances affecting one portion of the alimentary canal by reflex and sympathetic action, lead to disturbances in other portions, and it is this reflex disturbance which makes a study of the tongue so valuable clinically.

Another group of cases in which we get a similar diminution comprises those conditions in which there is excessive watery secretion and drain from the blood : in cholera, in which the drain is into the intestinal canal, in diabetes, and in chronic interstitial nephritis in which there is great pouring out of fluid through the kidneys. Yet another category is included in those cases in which there is paralysis of the 7th nerve and of the secretory nerves of the salivary glands. Experimentally, Heidenhain has pointed out

that after section of the nerves passing to the parotid and submaxillary, there develops after twelve hours a thin watery secretion from the glands—the so-called paralytic secretion. The exact mechanism of the secretion is unknown, and as above stated is independent of the nerves. This continues for about three weeks and then ceases, its cessation is found to be due to a progressive degeneration of the gland cells ending in complete atrophy.

Alterations in Composition of the Saliva.

The normal saliva is slightly alkaline, and under certain conditions not very well understood either at the moment of secretion or later through the fermentation process set up by bacteria in the mouth, noticeably by those producing lactic acid associated with a milk diet, the saliva may become acid; in this slightly acid medium we have a condition favouring the growth of moulds rather than bacteria. Thus we find that in weakly children and again in older people exhausted by long continued illness, with the acidity of the saliva there may be an extensive growth of mould on the surface of the tongue and in the mouth generally, extending down the pharynx and the œsophagus, the most common cause of this condition being, the oïdium albicans or thrush fungus. This, in itself, seems to exert no very extensive constitutional disturbance, though occasionally the growth is not only on the surface, but extends into the superficial layers of the mucous membrane. It is an indication of a greatly lowered constitutional condition rather than a primary cause of the same.

Other Causes. There may be relative or complete absence of the ferment. This, judging from my own experience, seems to lead to no disturbance. Occasionally we have abnormal constituents; bile in the case of jaundice; urea, in the latest stages of nephritis; extremely rarely do we find in diabetes the secretion of sugar. (This difference between urea and sugar, both of them very diffusible substances, is a good example of the selective action of the vessels and glands..... Certain drugs, like iodine, may also appear in the saliva while in certain obscure conditions cyanides may be present in increased quantities.

FAUCES.

In connection with the fauces, the main conditions leading to general systemic disturbance are, as might be expected, in connection with the muscular system. Derangements in the actions of these muscles leading to impairment or arrest of deglutition. I need scarcely say that the muscles of the fauces have, to a very large extent, an involuntary action and are out of the control of the will; it is the presence of the bolus of food which normally causes their contraction in such a way as to force that food down into the œsophagus. It will thus be understood that in the first place, we may have conditions in which a reflex stimulus causes these muscles to work either prematurely or irregularly. This is well marked in conditions of hydrophobia, tetanus, and strychnin poisoning, where, upon passage of food into the mouth, the muscles contract so rapidly and so powerfully, that before the food reaches their neighborhood that food cannot pass down into the œsophagus. On the other hand, certain poisons, more especially of the narcotic type like, morphia, may so lessen reflex irritability that the food passes into the mouth, the muscles do not contract, and deglutition is prevented. Certain groups of the muscles may be paralyzed, and as a result instead of the food being forced down the œsophagus, it finds its way into the posterior nares, and may find its way also into the trachea, and may further set up aspiration pneumonia in the lungs. This is well seen in the pharyngeal abscesses or transient paralysis following upon diphtheria.

OESOPHAGUS.—The œsophagus serves only as a passive tube carrying the food from the mouth into the stomach. The only conditions which here need be considered are those which lead to the obstruction of the tube and to consequent difficulty of passage of food into the stomach, and inasmuch as the digestive process and the absorption of that food only takes place after the œsophagus has been passed, it follows that any such obstruction, if partial, inevitably leads to malnutrition and emaciation; if complete, to slow but certain death from starvation. Such obstruction may occur from foreign bodies or growths within the lumen of the

œsophagus; from inflammation or new growths within the walls of the œsophagus leading to the constriction of the tube; from pressure and occlusion acting from without; tumours, abscesses or aneurysms of the surrounding tissues.

We may here note that constriction or obstruction of the œsophagus leads to a dilatation of the tube above the point of obstruction, which may be very marked and which, as in similar conditions of dilatation of the stomach, may be associated with periodic regurgitation and vomiting of the food accumulating above the point of obstruction.

Paralysis or functional incapacity of the œsophageal muscle is very rare, and, as can be understood, it is a very fatal condition. Experimentally, as Cohnheim points out, if both vagi be cut in the rabbit, 24 hours after the operation the animal dies, and the gullet is found blocked with the pulp of the food that has been eaten and which has not been passed on into the stomach.

Rupture of the wall of the œsophagus naturally leads to death within a few hours, on account of the inflammation and disturbance set up by the passage of fluid and food into the mediastinum and sometimes into the pleural cavity. Spontaneous rupture apparently occurs occasionally, and Zenker attributes the condition to a softening of the wall possibly by regurgitation of gastric juice.

Diverticulum of the œsophagus is of more frequent occurrence and may be of two forms: (1) Congenital, the so-called Pulsion Diverticulum, generally upon the posterior aspect of the œsophagus and brought about by congenital weakness of the muscular coat. At the point of weakening, the pressure of the other muscles upon the bolus of food causes the weakened area to be dilated outwards, and gradually this extension of the coat at the point becomes greater and greater until a large sac may be produced in which the mass of food becomes retained, and it may reach such size as by pressure cause partial occlusion of the œsophagus. The other form (2) the Traction Diverticulum is in general small and in most cases situated at the level of the bifurcation of the treachea. These are brought about by inflammation of the peritracheal lymph glands with adhesion to the œsophagus, cicatrisation and production in this way of small funnel shaped diverticula.

THE STOMACH.

In discussing the effects of disease of the stomach on the rest of the organism, we recognize in the first place that the most important series of disorders naturally are associated with alterations in the amount and in the quality of the gastric juice, the all-important agent in gastric digestion. At the same time it must be remembered that to a less extent it is true than is the case with the salivary secretion, the gastric secretion is not the most important factor in digestion. The main digestive process is brought about by the pancreatic juice, the gastric juice playing a very important part in breaking down the food into small particles so that it becomes more easily acted upon in the intestines. Thus it happens that now and then we come across cases in which the stomach is congenitally so small that it will only hold an ounce or two, and yet life may have continued for years, and other cases in which through infiltrating carcinoma of the walls, the organ becomes reduced to little more than a tube some four or five inches in length, while experimentally and, of late, surgically, it has been shown that life can be continued with fair comfort and for long periods when the stomach has been totally extirpated. In this last case great care has to be taken that the food to be assimilated is already in a soft, semi-fluid state, any solid food being liable to cause, not only indigestion, but great irritation of the intestinal tract. Thus, while admitting that a considerable amount of absorption does take place from the stomach, we must recognize this organ as being in the main the region in which the food is prepared for subsequent assimilation.

With regard to the gastric juice, as with the saliva, so here we may have alterations in quantity and alterations in constitution; the most important feature clinically in the gastric juice would appear to be the free hydrochloric acid, for in general it may be stated that the amount of secretion and the amount of acid produced go hand in hand. On the other hand there may be considerable variation in the secretion in general, and it is held nowadays that different forms of food in

this may bring about, not only different amounts of secretion, but differences in the composition of the secreted juice. Under certain conditions we obtain marked increase in the amount of juice, and Reichmann has described a special form of gastric disturbance in which there is a large increase in the amount of juice produced, together with increase in the amount of acid. Such increase accompanied by hyperacidity, has frequently been noted in cases of gastric ulcer. When the stomach is emptied we may come across increase of the hyperchloric acid to as much as 0.3 per cent., if the amount reaches 0.4 per cent. there is great gastric discomfort, not to say pain, there is a tendency to vomit and a condition of very marked "Dyspepsia." Such increase is found in hysterical conditions, and has been noticed again periodically in Tabes Dorsalis.

Diminution in the amount of gastric juice and in the acid secreted is well marked in cases of both chronic and acute gastritis; in amyloid degeneration of the organ, in gastric cancer, in various forms of infection, and in grave anæmic conditions. In all of these conditions the pepsin fails along with the acid; as a result in the first place, there is arrest of the process of digestion in the organ, and food taken in remains for long in a more or less solid condition and is not allowed to pass the pylorus. In the second place the absence of the acid leads to a proliferation of various bacteria and yeasts. In consequence of this, if the irritating disturbance be kept up for long, the modified contents of the stomach react upon the walls of the organ leading to degeneration of the mucosa, and thus there may be set up a vicious circle.

With the degeneration of the mucosa, the secreted juice is impoverished, and is abnormal in quality, digestion again becomes further impaired, and, remembering that if the solid food be not properly broken up through the action of the juice, it is not passed forward, we thus get a greater and greater accumulation of material in the stomach, and this together with distension of the organ by the gases given off by the fermenting material, leads to a condition of great dilatation of the organ, and that dilatation is accompanied by weakening of the muscle fibres, so that another function

of the stomach, namely, peristalsis, and the propulsion of food, is impaired, and with this again the condition is liable to go on from bad to worse, each stage in this process rendering proper digestion more and more impossible. But not only does this process tell upon the stomach itself, but in various ways influences the general condition of the individual for the worse. In the first place, such fermented or putrefied contents of the stomach gaining entrance into the duodenum there, when they reach the alkaline secretion of pancreas become the seat of abondant bacterial growth.

TABLE OF CONTENTS.